EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2018
EMA/CHMP/302652/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sprycel

International non-proprietary name: dasatinib

Procedure No. EMEA/H/C/000709/X/0056/G

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

BE Bioequivalence

CQA Critical Quality Attribute

FMEA Failure mode effects analysis

GRAS Generally recognized as safe

HPLC High performance liquid chromatography

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IR-ATR Infrared attenuated total reflection

PFOS Powder for oral suspension

Ph. Eur. European Pharmacopoeia

PIBA Press in bottle adapter

PIP Paediatric Investigation Plan

QTPP Quality target product profile

SmPC Summary of Product Characteristics

TAMC Total Aerobic Microbial Count

TSE Transmissible Spongiform Encephalopathy

TYMC Total Combined Yeasts/Moulds Count

1. Background information on the procedure

1.1. Submission of the dossier

Bristol-Myers Squibb Pharma EEIG submitted on 26 April 2017 a group of variations consisting of extensions of the marketing authorisation concerning:

- a new pharmaceutical form (powder for oral suspension) associated with a new strength (10 mg/ml) indicated in the treatment of paediatric patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML CP), or with Ph+ CML CP resistant or intolerant to prior therapy including imatinib

and the following variation:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

To include the treatment of paediatric patients with newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib for Sprycel film-coated tablets. Sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the new indication and its relevant posology, to add a warning on effects on growth and development in the paediatric population and to update the safety information.

The Annex A, Annex II, Labelling, Package Leaflet and RMP (version 15.3) are updated in accordance.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Sprycel was designated as an orphan medicinal product EU/3/05/339 on 23 December 2005 in the following condition: treatment of chronic myeloid leukaemia. However, the orphan designation expired on 22 November 2016.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0118/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0118/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific Advice/Protocol Assistance

The MAH received Scientific Advice/Protocol Assistance from the CHMP on 21 October 2004, 19 July 2007, 18 November 2010, 17 February 2011 and 18 October 2012. The Scientific Advice/Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Fátima Ventura

- The application was received by the EMA on 26 April 2017.
- The procedure started on 18 May 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 August 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 7 August 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 7 August 2017.
- During the meeting on 1 September 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 14 September 2017, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 21 December 2017.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on 30 January 2018.
- During the PRAC meeting on 5-8 February 2018, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 22 February 2018, the CHMP agreed on a list of outstanding issues to be sent to the MAH.
- MAH submitted the responses to the CHMP List of Outstanding Issues on 26 March 2018.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 6 April 2018.
- During the meeting on 23-26 April 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for extensions of the marketing authorisation for Sprycel.
- The CHMP adopted a report on non-similarity of Sprycel with Tasigna and Iclusig on 26 April 2017 (Appendix 1).

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant requested the approval for the following indication:

Sprycel is indicated for the treatment of children and adolescents aged 1 year to 18 years with Ph+ chronic phase CML.

2.1.2. Epidemiology and risk factors, screening tools/prevention

CML is relatively rare in both adults and children, with rates increasing with increased age; rates peak in the age range of 65-74 years. The incidence of the disease in paediatric patients increases in teen years: CML constitutes 2% of all leukemias in children younger than 15 years and 9% of all leukemias in adolescents between 15 and 19 years, with an annual incidence of 1 and 2.2 cases per million in these two age groups, respectively. An estimated 12-14% of paediatric and young adult patients die within 5 years of CML diagnosis. Overall, the genetic basis and course of disease is similar in adult and paediatric CML patients. Children and adolescents tend to have a more aggressive clinical presentation than older adults, although the impact of this feature on progression and response to treatment in paediatric patients remains unknown.

Exposure to ionizing radiation is the only known risk factor. While there is no known familial disposition to CML, rare families in which multiple members develop MPNs, including CML, have been described.

2.1.3. Aetiology and pathogenesis

Chronic myeloid leukemia is a clonal myeloproliferative neoplasm derived from an abnormal multipotent hematopoietic stem cell that has acquired the BCR-ABL1 fusion gene, usually through t(9;22)(q34;q11), also known as the Philadelphia chromosome. The development of chronic phase CML appears to be a direct result of BCR-ABL1 activity, which promotes its development by allowing: uncontrolled proliferation of transformed cells; discordant maturation; escape from apoptosis; altered interaction with the cellular matrix.

The progression of CML from chronic phase to accelerated phase or blast crisis is a complex, multistep process, but also appears to involve the constitutive expression of the BCR-ABL1 tyrosine kinase.

The following events appear to be necessary for the transformation of chronic phase CML into an acute phase of disease: Constitutive expression of the BCR-ABL1 tyrosine kinase; Differentiation arrest; Genetic instability and additional chromosomal abnormalities; Inactivation of tumor suppressor genes

Mouse models have provided support for BCR-ABL1 as the principal cause of these malignancies and have allowed for the in vivo study of BCR-ABL1 signaling, identification of novel genes involved in CML development, and testing of potential therapies.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

CML has a triphasic or biphasic clinical course: a chronic phase, which is present at the time of diagnosis in approximately 85 percent of patients; an accelerated phase, in which neutrophil

differentiation becomes progressively impaired and leukocyte counts are more difficult to control with treatment; and blast crisis, a condition resembling acute leukemia in which myeloid or lymphoid blasts proliferate in an uncontrolled manner.

The clinical findings at diagnosis of CML vary among reported series and also depend upon the stage of disease at diagnosis. Twenty to 50 percent of patients are asymptomatic, with the disease first being suspected from routine blood tests. Among symptomatic patients, systemic symptoms such as fatigue, malaise, weight loss, excessive sweating, abdominal fullness and bleeding episodes due to platelet dysfunction are common.

Abdominal pain and discomfort may include left upper quadrant pain (sometimes referred to the left shoulder) and early satiety, due to the enlarged spleen with or without peri-splenitis and/or splenic infarction. Tenderness over the lower sternum, due to an expanding bone marrow, is sometimes seen. Acute gouty arthritis may also present at this time, due to overproduction of uric acid.

Other frequent findings include splenomegaly, anemia, white blood cell count above 100,000/microL and platelet count above 600,000 to 700,000/microL. Involvement of extramedullary tissues such as the lymph nodes, skin, and soft tissues is generally limited to patients with blast crisis.

The peripheral smear typically demonstrates a leukocytosis with a median white count of approximately 100,000/microL. The white blood cell differential typically shows virtually all cells of the neutrophilic series, from myeloblasts to mature neutrophils with peaks in the percent myelocytes and segmented neutrophils. Blasts typically account for less than 2 percent. The presence of a greater percent of myelocytes than the more mature metamyelocytes ("leukemic hiatus" or "myelocyte bulge") is one of the classic findings in CML. The granulocytes of chronic phase are morphologically normal with no evidence of dysplasia, but dysplasia can develop in more advanced disease, and particularly in accelerated phase.

Bone marrow aspiration and biopsy demonstrates granulocytic hyperplasia with a maturation pattern that reflects that seen in the peripheral smear. Other non-specific bone marrow findings include an increase in reticulin fibrosis and vascularity.

The peripheral blood and bone marrow aspirate differential count are key components of determining the disease stage. In general, peripheral blood and bone marrow blasts between 10 and 19 percent are diagnostic of accelerated phase disease, while blasts over 20 percent are diagnostic of blast crisis.

The vast majority of patients (90% to 95%) demonstrate the t(9;22)(q34;q11.2) reciprocal translocation that results in the Ph chromosome.

Various scoring systems have also been devised in an attempt to predict disease outcome. While the Sokal and Euro (Hasford) scores were developed prior to the discovery of imatinib, the EUTOS score was developed and validated using data from 2060 patients enrolled in prospective studies of imatinib and is intended to be a better predictor of clinical responses to that drug. High-risk patients defined by this scoring system have a one in three chance of failing to respond to imatinib.

2.1.5. Management

In the EU (European Union), imatinib (Glivec) is indicated for the treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment; adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis and adult and paediatric patients with newly diagnosed

Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.

In addition, Tasigna was approved for the treatment of paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase and paediatric patients with chronic phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib.

There is a high unmet medical need for approved therapies that can improve responses in paediatric patients with CML-CP who received imatinib as first-line treatment. Approximately 10% to 30% of adult and paediatric patients with CML-CP discontinue from imatinib due to declining response to treatment, progression of disease, or intolerance of adverse drug effects. Options are also needed for newly-diagnosed subjects and before considering HSCT. Paediatric patients with no suitable donor for HSCT have an even more critical unmet need for disease management.

About the product

Dasatinib inhibits the activity of the BCR ABL kinase and SRC family kinases along with a number of other selected oncogenic kinases including c KIT, ephrin (EPH) receptor kinases, and PDGFβ receptor. Dasatinib is a potent, subnanomolar inhibitor of the BCR ABL kinase with potency at concentration of 0.6 0.8 nM. It binds to both the inactive and active conformations of the BCR ABL enzyme (SmPC section 5.1).

The recommended starting daily dosage of Sprycel powder for oral suspension for paediatric patients and adult patients who cannot swallow tablets is shown in **Table 1** (SmPC section 4.2).

Table 1: Dosage of Sprycel powder for oral suspension for patients with Ph+ CML-CP (10 mg/mL suspension upon constitution)

Body Weight (kg)	Daily Dose, mL (mg)
5 to less than 10 kg	4 mL (40 mg)
10 to less than 20 kg	6 mL (60 mg)
20 to less than 30 kg	9 mL (90 mg)
30 to less than 45 kg	10.5 mL (105 mg)
at least 45 kg	12 mL (120 mg)

Type of Application and aspects on development

The applicant requested the approval for the following indication:

Sprycel is indicated for the treatment of children and adolescents aged 1 year to 18 years with Ph+ chronic phase CML.

The indication approved by the CHMP was as follows: Sprycel is indicated for the treatment of paediatric patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukemia (CML) in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib (SmPC, section 4.1).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as powder for oral suspension containing 10 mg/ml of dasatinib (as monohydrate) as active substance.

Other ingredients are: sucrose, carmellose sodium, simethicone emulsion (consisting of simethicone, polyethylene glycol sorbitan tristearate, polyethoxylate stearate, glycerides, methylcellulose, xanthan gum, benzoic acid, sorbic acid, sulfuric acid), tartaric acid, trisodium citrate anhydrous, sodium benzoate (E211), silica hydrophobic colloidal, and mixed berry flavour containing benzyl alcohol, sulphur dioxide (E 220).

The product is available in high density polyethylene bottle with polypropylene child-resistant closure as described in section 6.5 of the SmPC. Each pack also contains a low density polyethylene press-in-bottle adapter (PIBA) and an oral dosing syringe (polypropylene syringe barrel with high density polyethylene syringe plunger rod) in a sealed plastic bag.

2.2.2. Active Substance

The active substance used to manufacture the new pharmaceutical form: oral suspension is the same as that used in the manufacture of the currently authorised Sprycel film-coated tablets (EU/1/06/363/001-015).

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is a powder for oral suspension (PFOS) containing 0.99 g (10 mg/ml after constitution) of the active substance.

In accordance with the PIP which includes the requirement of an age-appropriate formulation, the marketing authorisation holder has formulated a taste-optimized oral suspension product (powder for oral suspension). The goal of the development of the powder for oral suspension was to provide a stable, palatable, and dose uniform suspension at a concentration of 10 mg/mL upon constitution with water. In the selection of formulations for evaluation, consideration was given to the preferred dosage forms as outlined in the EMA Reflection Paper, Formulations of Choice for the Paediatric Population. Solution and suspension formulations were considered to be preferable over other dosage forms such as powders or chewable tablets in the targeted age group of 1 to 6 years, since they are most acceptable for children who are not yet able to chew or swallow and they provide for greater flexibility in delivering variable doses. Feasibility of different formulation approaches were evaluated, including a ready to-use solution and powder for oral solution, however, these formulation approaches were not pursued due to limited solubility of dasatinib in the vehicles and taste-masking challenges.

The powder will be constituted with water at the pharmacy and provided to the patient as a multi-dose product presentation with press-in-bottle adaptor and oral dosing syringe.

The active substance used is the crystalline monohydrate form, which is the same as that used in the marketed film-coated tablets. Quality risk assessments and experiments were performed to understand the compositional requirements for a robust formulation and the impact of manufacturing

process parameters on the identified critical quality attributes (CQAs). Several commonly used excipients for powder for oral solution/suspension were evaluated as binary mixtures (with or without water) for compatibility with dasatinib. The levels of individual and total impurities were monitored. Dasatinib was prone to significant degradation in the presence of certain excipients. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards with the exception of mixed berry flavour. All flavour ingredients contained in the mixed berry flavour are recognized as safe (GRAS). In addition, the constituents of the mixed berry flavour are listed in the EU list of flavouring substances as defined by Regulation EU 872/2012. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Formulation development studies were performed to select the type and level of the excipients for a palatable formulation, which, when constituted with water, would be easily dispersed and dispensed by the patient/care giver using the supplied oral dosing syringe.

During formulation development palatability and taste, selection of sweetener, selection of pH/buffer system, suspending agents, preservation system (and level), antifoaming agent, flavouring agent, constitution time and re-dispersibility time, and particle size were studied. Characteristics such as the pH solubility/stability profile of the active substance, chemical compatibility, and taste led to the use of the tartrate-based buffer system at a pH where the selected preservative is effective. Other excipients providing desired product profile performance and manufacturability were selected for evaluation based on the drug-excipient compatibility study and the amount required was confirmed during the development studies.

Formulation comparability studies were provided. An open-label crossover bioequivalence (BE) study was conducted in fasted adult healthy subjects to compare the bioavailability of reference tablets, dasatinib PFOS and dispersed tablets

The applicant has applied QbD principles in the development of the finished product. However, no design spaces were claimed for the manufacturing process of the finished product

The proposed commercial manufacturing process was designed to consistently meet the identified finished product critical quality attributes (CQAs). Risk assessments were performed at multiple stages throughout development to guide development studies and to establish the control strategy for the commercial manufacturing process. The process development studies evaluated different manufacturing process parameters to determine the effect on selected product attributes. The powder blend is manufactured using a series of milling and blending steps followed by filling of the final powder blend into bottles. Initial selection of the processing steps and parameters was based upon prior knowledge and experiences gained from other powder finished products.

Manufacturing process risk assessments throughout process development to determine the potential failure modes associated with the manufacturing process and to quantify the level of risk to the product quality attributes were employed. The risk assessments are used to guide the design of the process development studies so that appropriate controls and/or mitigation measures can be identified and implemented to minimize the risk to an acceptable level. For the proposed commercial process, process risk assessments using Failure Mode and Effect Analysis (FMEA) were conducted to identify the level of risk in the manufacturing process

Dasatinib PFOS is supplied in a 120 mL high density polyethylene bottle (with polypropylene child-resistant closure). Each pack also contains a low density polyethylene press-in-bottle adapter (PIBA) and a 12-mL oral dosing syringe (polypropylene syringe barrel with high density polyethylene syringe plunger rod) in a sealed plastic bag. The material complies with Ph Eur and EC requirements. The

choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The syringe is CE marked.

Manufacture of the product and process controls

The manufacturing process consists of 3 main steps: preparation of milled sucrose-simethicone mixture, preparation of milled sucrose, and preparation of final blend, filling and, packaging and labelling operation

A simple validation protocol is provided. No validation is provided for pilot or commercial batches. The prospective process validation will be completed prior to the launch of the commercial product. The validation batches will be processed according to an approved manufacturing batch record and per an approved process validation protocol. During the validation study, process steps will be monitored and the results will be documented in a process validation report. The manufacturing process of the product is considered as standard process, therefore, it is accepted that only the validation protocol suffices and that no actual process validation is provided in the dossier.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description of powder (visual), description of suspension (visual), identification (HPLC, Raman, IR-ATR), assay (HPLC), impurities/degradants (HPLC), dissolution (HPLC), uniformity of mass (Ph Eur), pH, sodium benzoate (HPLC) and microbial limits (TAMC, TYMC, *Escherichia Coli*).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The reference standard used in the analysis of the finished product is the same as used for the active substance. Satisfactory information regarding the reference standards used has been presented.

Batch analysis results are provided for 8 commercial batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 24 months under long term conditions (5 °C, 25 °C / 60% RH, and 30 °C / 75%RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, appearance of the suspension, assay, impurities, sodium benzoate, dissolution, water content, pH, constitution time, identity and microbial limits (TAMC, TYMC, *Escherichia Coli*). The analytical procedures used are stability indicating.

The finished product shows little or no change in long term stability studies. All results meet the proposed acceptance criteria. In addition, stress stability studies (-20°C, 50°C, open bottle, and

freeze/thaw temperature cycling) were performed in one batch. All results meet the proposed acceptance criteria.

One batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The photostability study results indicate that the product does not need to be protected from light.

In-use constitution studies were performed in 3 batches at the initial and 12 month time points. Finished product bottles were constituted with purified water, and stored for up to 2 months at 5 °C, 30 °C/75% RH, and for 1 month at 40°C/75%RH (initial time point only) and then tested. There was essentially little to no change observed and all results met the proposed acceptance criteria.

In-use studies were also performed in 3 batches at the initial and 12 month time points for constituted finished product. Bottles were constituted with water and stored at 5°C and 30°C/75%RH. The individual bottles were tested at initial and 30 days. There was essentially little to no change observed. The test results for both the initial and 12-month in-use studies remained essentially unchanged when compared with the zero-time values at the initial use-time studies.

Food mixing studies were performed on the PFOS at initial and at 9 months (stored at 30 °C/75% RH) using 4 different vehicles for mixing with the constituted dasatinib PFOS, 10 mg/mL. The constituted suspension was first stored for 2 months (60 days) at 30 °C/75% RH, then 2 mL of the constituted suspension was mixed with 15 grams of liquid or food/vehicle, and stored for up to 2 hours at 30 °C/75% RH and then tested. There was essentially little to no change observed in assay (% of initial), impurities, and dissolution for suspension mixed with food/liquid through 2 hours of storage at 30 °C/75% RH. Results remained essentially unchanged at the initial and 9-month time points.

Based on available stability data, the proposed shelf-life of the power is of 24 months stored bellow 25 °C , after constitution, the oral suspension is stable for 60 days when stored in a refrigerator (2 °C – to 8 °C) and do not freeze as stated in the SmPC (section 6.3) are acceptable. Constituted oral suspension may be mixed with milk, yogurt, apple juice, or apple sauce and may be stored at or below 25 °C for up to 1 hour.

Adventitious agents

Sucrose is the only specified risk material of animal origin, used as an excipient in the finished product. In the processing of sucrose, the manufacturer uses animal bone-charcoal as a filtering agent to decolorize the raw sugar and to produce white sugar crystals. TSE/BSE "risk free" declaration for animal charcoal used in the manufacturing process of sucrose was provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product. However, no design space was claimed.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

No applicable

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.1. Ecotoxicity/environmental risk assessment

The applicant estimated new PECs for surface, groundwater, waste water treatment plant as well as sediment and calculated the possible environmental risks taking into account the PNECs assessed previously – to account for the potential increase in use of the product.

The current risk assessment conclusions for dasatinib to the different environmental compartments are presented in Table 2 below:

Table 2: Summary of main study results

Substance (INN/Invented Name): Dasatinib			
CAS-number (if available): 863127-77-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH 5 – 1.85 pH 7,8 – 3.56 pH 9 - 3.56	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	1.85 - 3.56	not B
	BCF	BCF<5	not B
Persistence	DT50 or ready biodegradability	Dasatinib was not readily biodegradable at 28 days	P
Toxicity	NOEC or CMR	-	-
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	1.8	µg/L	> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 302A	K_{oc} =2430	
Ready Biodegradability Test	OECD 302A	half-life of 5.4 hours	But is not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic	OECD 308	$DT_{50, water}$ =3.5-4 days $DT_{50, sediment}$ = NA	

Sediment systems		$DT_{50,\ whole\ system}$ =79.7-131 days % shifting to sediment = 27.1-56.3			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	73	µg/L	*Pseudokirchneriella Subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	68	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	18	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	EC50 > 1000 000	µg/L	Highest dose tested
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	2.6-2.8	L/kg	%lipids: 2.32-3.64% wet weight tissue basis
Sediment dwelling organism		NOEC	100	mg/kg	*Chironomus Riparius*

2.3.2. Discussion on non-clinical aspects

No additional nonclinical toxicology studies were conducted with dasatinib in view of the paediatric indications, which is consistent with the ICH S9 guidance that states that a dedicated nonclinical toxicology study in juvenile animals is not needed to support a paediatric registration of anticancer drugs. This approach is considered acceptable.

An updated environmental risk assessment was submitted, however further information should be gathered from an OECD 106 study in 3 soils; this is recommended to be provided post-authorisation.

2.3.3. Conclusion on non-clinical aspects

Existing non-clinical data with dasatinib are sufficient to cover the new pharmaceutical formulation and use in paediatric CML patients; no new data were necessary.

The MAH is recommended to submit additional information on the ERA following the completion of an OECD 106 study in 3 soils.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community

were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 3: Studies Supporting the Efficacy of Dasatinib in Paediatric Subjects with Chronic Myeloid Leukaemia

Study	Study Description	Ph+ Leukaemia Strata/Cohorts	Subjects Planned	Subjects Treated	Dasatinib Dose and Regimen	Primary Objectives	Database Lock and CSR Dates
CA180038 (Children's Oncology Group study Protocol ADVL0516)	Phase 1, open-label, multi-center study of dasatinib in paediatric subjects with recurrent/ refractory solid tumors or imatinib-resistant Ph+ leukaemia.	**Stratum 2** Imatinib-resistant or intolerant Ph+ leukaemia: Ph+ CML Ph+ ALL	≤ 24 total, ≤ 12 per dose level	11 9 2	Dose levels: 50, 65, and 85 mg/m^2 BID Formulation: oral tablet Dose course = 28 days, repeated every 28 days up to 24 courses if the subject had at least stable disease and met laboratory criteria as defined in the protocol.	Describe and define the toxicities of dasatinib administered as an oral agent given twice daily in children with imatinib-resistant Ph+ leukaemia. Characterize the PK of dasatinib in children with refractory solid tumors and imatinib-resistant Ph+ leukaemia.	First patient first visit: 05-Jun-2006 Study close date: 26-Sep-2008 Last patient last visit: 07-Feb-2009 Final CSR: 08-Dec-2009 Study status: completed
CA180018 (Protocol ITCC 005)	Phase 1, open-label, dose-escalation (3+3 design, intra-subject dose escalation) study of children and adolescents with relapsed/refractory leukaemia treated with dasatinib orally QD until disease progression, death, intolerable toxicity, or patient/physician preference.	**Stratum 1** Imatinib-resistant or intolerant Ph+ CML-CP	18	17	Starting dose: 60/80 mg/m^2 QD Dose escalation: up to 120 mg/m^2 QD Formulation: oral tablet Dose course = 21 days	To establish, by stratum using a dose-finding design, a recommended Phase 2 dose of dasatinib in children and adolescents with relapsed or refractory leukaemia.	First patient first visit: 21-Mar-2006 Database lock: 28-Jun-2011 Final CSR: 04-Nov-2011 Database lock: 04-Nov-2016 Addendum CSR: 01-Mar-2017 Study status: ongoing
		Stratum 2/3 Advanced Ph+ leukaemias: Imatinib-resistant or -intolerant AP-CML Imatinib-resistant or -intolerant LBP-CML Relapsed/refractory ALL after imatinib use	20	17 2 1 14	Starting dose: 60/80 mg/m^2 QD Dose escalation: up to 120 mg/m^2 QD Formulation: oral tablet Dose course = 21 days		

Study	Study Description	Ph+ Leukaemia Strata/Cohorts	Subjects Planned	Subjects Treated	Dasatinib Dose and Regimen	Primary Objectives	Database Lock and CSR Dates
CA180226	A Phase 2, open-label, non-randomized, multi-center trial involving subjects with newly diagnosed CML who were treatment-naive and subjects with CML-CP, Ph+ ALL, AP-CML, or BP-CML who relapsed after, or were resistant or intolerant to, imatinib treatment. Subjects were treated until disease progression, death, intolerable toxicity, or patient/physician preference.	**Cohort 1**: Imatinib-resistant or intolerant Ph+ CML-CP	25	29	Dose: 60 mg/m^2 QD Formulation: oral tablet	To estimate the rate of MCyR to dasatinib therapy in children and adolescents with CML-CP who proved resistant or intolerant to imatinib.	Study start date: 20-Mar-2009 Last patient last visit for 2-year analysis: 01-Sep-2016 Database lock: 04-Nov-2016 Final CSR: 01-Feb-2017 Study status: ongoing
		Cohort 2 Advanced Ph+ leukaemias: • Imatinib-resistant or -intolerant AP-CML • Imatinib-resistant or -intolerant BP-CML • Relapsed/refractory ALL after imatinib use	17	17 0 8 9	Dose: 80 mg/m^2 QD Formulation: oral tablet	To estimate the CHR rate in children and adolescents with Ph+ ALL, AP-CML, and BP-CML, who were resistant to, intolerant to, or who relapsed after prior imatinib therapy.	
		Cohort 3: Newly diagnosed treatment-naive Ph+ CML-CP **Cohort 3a** (tablet)	80 50	84 51	Dose: 60 mg/m^2 QD Formulation: oral tablet	To estimate the rate of CCyR to dasatinib therapy in children and adolescents with newly diagnosed CML-CP who are treatment-naïve (except HU).	
		Cohort 3b (PFOS)	30	33	Dose: 72 mg/m^2 QD Formulation: PFOS (first 12 months, then could switch to tablet)		

Abbreviations: ALL = acute lymphocytic leukaemia; AP = accelerated phase; BID = twice daily; BP = blast phase; CCyR = complete cytogenetic response; CHR = complete hematologic response; CML = chronic myeloid leukaemia; CP = chronic phase; HU = hydroxyurea; LBP = lymphoid blast phase; MCyR = major cytogenetic response; PFOS = powder for oral suspension; Ph+ = Philadelphia chromosome positive; QD = once daily.

2.4.2. Pharmacokinetics

Absorption

Bioequivalence (BE) study CA180352

Study CA180352 was an open-label, randomized, 3-period, 3- treatment crossover study conducted in healthy adult subjects to compare the dasatinib PFOS to the intact tablet formulation as well as the same tablet formulation dispersed in orange juice. There were 77 subjects completed the study. PK samples were collected predose (0), 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 18 and 24 hours post dose.

Taste assessments of the PFOS were made 10 seconds and 1 minute after administration.

Plasma PK parameters for dasatinib following a single oral dose of 100 mg administered as an intact tablet (Treatment A), PFOS (Treatment B) or dispersed tablet (Treatment C) for 77 subjects are summarized in **Table 4**.

Table 4: Pharmacokinetic Parameters for Dasatinib following Intact Tablet, PFOS and Dispersed Tablet (CA180352)

Treatment	Cmax (ng/mL) GM [n] (CV%)	AUC(0-T) (ng•h/mL) GM [n] (CV%)	AUC(INF) (ng•h/mL) GM [n] (CV%)	Tmax (h) Median [n] (Min-Max)	T-HALF (h) Mean [n] (SD)
A	114 [78] (51)	374 [78] (45)	429 [75][a] (39)	1.00 [78] (0.25 - 3.00)	4.96 [75][a] (1.31)
B	106 [77] (53)	327 [77] (44)	338 [77] (43)	0.53 [77] (0.50 – 3.00)	4.82 [77] (1.17)
C	110 [77] (50)	342 [77] (42)	353 [77] (41)	0.50 [77] (0.50 – 4.00)	4.91 [77] (1.25)

Treatment A: A single oral dose of dasatinib, 100 mg as reference tablet (2 x 50 mg tablets).
Treatment B: A single oral dose of dasatinib, 100 mg administered as dasatinib PFOS (10 mg dasatinib/mL).
Treatment C: A single oral dose of dasatinib, 100 mg as dispersed tablets in orange juice.

The bioequivalence analyses are provided in

Table 5: (PFOS and intact tablet), **Table 6** (dispersed tablet and intact tablet) and **Table 7** (PFOS and dispersed tablet).

Table 5: Bioequivalence Analysis of the PFOS and Intact Tablet (CA180352)

Treatment and Comparison	AUC(INF) (ng•h/mL) GM [n]	Cmax (ng/mL) GM [n]	AUC(0-T) (ng•h/mL) GM [n]
A	419 [75][a]	114 [78]	374 [78]
B	339 [77]	106 [77]	328 [77]
	Ratio of Adjusted GMs (90% CI)		
B vs A	0.808 (0.750, 0.869)	0.937 (0.822, 1.067)	0.878 (0.796, 0.967)

Treatment A: A single oral dose of dasatinib, 100 mg as reference tablet (2 x 50 mg tablets).
Treatment B: A single oral dose of dasatinib, 100 mg administered as PFOS.
[a] AUC(INF) could not be determined in 3 subjects (10052, 10057, and 10060) after receiving Treatment A.

Table 6: Bioequivalence Analysis of the Dispersed Tablet and Intact Tablet (CA180352)

Treatment and Comparison	AUC(INF) (ng•h/mL) GM [n]	Cmax (ng/mL) GM [n]	AUC(0-T) (ng•h/mL) GM [n]
A	419 [75][a]	114 [78]	374 [78]
C	354 [77]	110 [77]	342 [77]
	Ratio of Adjusted GMs (90% CI)		
C vs A	0.844 (0.784, 0.908)	0.967 (0.849, 1.102)	0.916 (0.831, 1.010)

Treatment A: A single oral dose of dasatinib,
Treatment C: A single oral dose of dasatinib, 100 mg as dispersed tablets in orange juice.
[a] AUC(INF) could not be determined in 3 subjects after receiving Treatment A.

Table 7: Bioequivalence Analysis of the PFOS and Dispersed Tablet (CA180352)

Treatment and Comparison	AUC(INF) (ng•h/mL) GM [n]	Cmax (ng/mL) GM [n]	AUC(0-T) (ng•h/mL) GM [n]
B	339 [77]	106 [77]	328 [77]
C	354 [77]	110 [77]	342 [77]
	Ratio of Adjusted GMs (90% CI)		
B vs C	0.957 (0.890, 1.029)	0.968 (0.850, 1.104)	0.958 (0.869, 1.056)

Treatment B: A single oral dose of dasatinib, 100 mg administered as PFOS.
Treatment C: A single oral dose of dasatinib, 100 mg as dispersed tablets in orange juice.

Post-hoc bioequivalence analysis in paediatric patients (CA180018)

The bioequivalence of dasatinib exposure between dispensed tablets and tablets was assessed by a post-hoc analysis in paediatric subjects (CA180018). The summary of dasatinib PK parameters by formulation in the paediatric study is presented in **Table 8**.

Table 8: Summary of Dasatinib PK in paediatric subjects by formulation

Treatment	Cmax (ng/mL) GM [n] (CV%)	AUC(0-T) (ng•h/mL) GM [n] (CV%)	AUC(INF) (ng•h/mL) GM [n] (CV%)	Tmax (h) Median[n] (Min-Max)	T-HALF (h) Mean [n] (SD)
Dispensed Tablet					
Infants/toddlers	1.0 [2] (15.2)	2.8 [2] (4.6)	3.2 [2] (17.7)	0.5 [2] (0)	2.1 [2] (0.5)
Children	2.2 [10] (72.6)	6.8 [10] (73.7)	6.6 [9] (74.0)	0.9 [10] (54.9)	2.7 [9] (1.9)
Adolescents	0.3 [1] (.)	0.6 [1] (.)	0.7 [1] (.)	0.5 [1] (.)	2.1 [1] (.)
Tablet					
Children	1.8 [33] (83.1)	5.9 [30] (103.8)	6.7 [27] (100.5)	1.4 [33] (55.2)	3.1 [27] (2.3)
Adolescents	1.1 [27] (67.2)	4.1 [27] (63.7)	4.6 [21] (63.7)	1.3 [27] (80.5)	3.9 [21] (1.8)

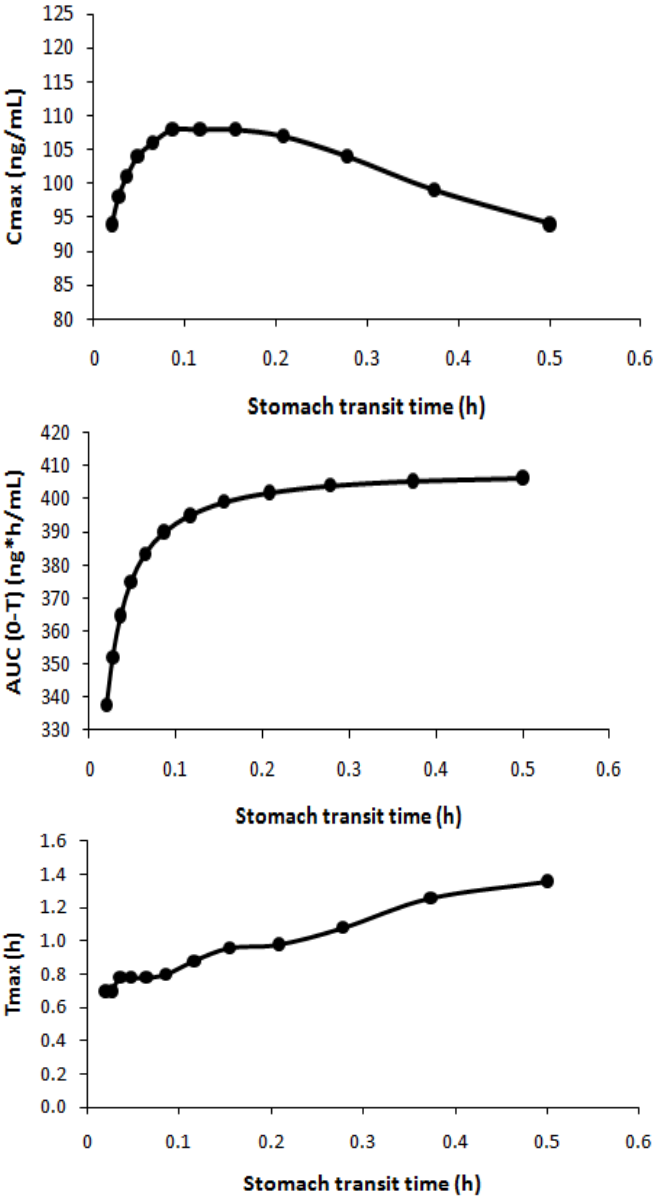
abbreviations: cv% coefficient of variation; gm=geometric mean; h=hour; max=maximum; min=minimum; n=number of non-missing observations; sd=standard deviation

PPK analysis of exposure differences between PFOS 72 mg/m^2 and tablet 60 mg/m^2 in paediatric subjects

The PPK analysis using pooled data from paediatric clinical studies was conducted to characterize dasatinib PK in paediatric subjects, and to quantify the differences in exposure produced by 72 mg/m^2 PFOS, relative to 60 mg/ m^2 tablet. The effect of formulation on dasatinib PK showed that the bioavailability of PFOS was approximately 40% lower than that of the tablet formulation in paediatric subjects. The bioavailability of PFOS (F_R) was 64.4% (95% CI 47.3% -87.8%) of the intact tablet, and the absorption rate (KA) was 120% (95% CI 67.5% -215%) of the tablet although with wide CI which also crossed 1.

PBPK simulation results for the gastric transit time sensitivity analysis of the suspension are presented in **Figure 1**.

Figure 1: Parameter Sensitivity Analysis of Stomach Transit Time on Cmax, AUC(0-T), and Tmax from PBPK Simulation



Abbreviations: AUC(0-T) = area under the plasma concentration-time curve from 0 to 24 hours, which was the last time point of the simulation; Cmax = maximum simulated plasma concentration; PBPK = physiologically based pharmacokinetic; Tmax = time of maximum simulated plasma concentration

Influence of food

In the paediatric Phase 1 study CA180018, no maximum tolerated dose (MTD) was identified across the tablet dose levels of 60 to 120 mg/m^2 QD. In the paediatric Phase 2 study CA180226, tablets or PFOS were administered irrespective of food intake, and the safety profile of dasatinib was consistent with the known safety profile in adult subjects with no clinically relevant safety concerns for paediatric subjects taking either tablet or PFOS during the first year of treatment.

Palatability studies of PFOS

Palatability of the PFOS formulation was assessed in studies CA180312 (at the time of manufacture), CA180447 (1 year manufacture) and CA180458 (2 years post-manufacture) by adult sensory

panellists, in study CA180352 by healthy adult subjects and also in Cohort 3b in study CA180226 by paediatric subjects with newly diagnosed CML-CP.

Specifically, the mixed berry-flavoured PFOS formulation was selected for further development, based on the results of assessing the taste properties of API prototype powder for oral solution (POS) and PFOS formulations. The dasatinib PFOS exhibited good flavour stability one-year and two-year post manufacture, both freshly constituted and after 30 and 60 days of room temperature storage.

In the BE study CA180352, healthy adult subjects were asked to evaluate the immediate taste (within the first 10 seconds) and the aftertaste (after 1 minute) of the PFOS using the Palatability Assessment, a 5-point taste rating scale (1 = extremely poor; 2 = poor; 3 = fair; 4 = good; 5 = excellent). The majority of subjects rated the taste of the PFOS as fair to excellent within 10 seconds of dosing.

In study CA180226, palatability assessments using a hedonic scale were conducted in conjunction with the morning dose of dasatinib PFOS in cohort 3b on Day 1 of Weeks 1, 2, 3 and 4. The assessment was completed by a caregiver for subjects younger than 6 years. Paediatric subjects older than 6 years completed the assessment independently. Subjects older than 6 years that could not complete the assessment independently were exempt from the palatability assessment.

Table 9: Frequency Distribution For Palatability Score (study CA180226)

	First Assessment N=29	Second Assessment N=28	Third Assessment N=28	Fourth Assessment N=28
Age <7 Years				
1	2 (6.9)	1 (3.6)	1 (3.6)	1 (3.6)
2	0	1 (3.6)	1 (3.6)	1 (3.6)
3	1 (3.4)	0	0	0
4	2 (6.9)	3 (10.7)	3 (10.7)	3 (10.7)
5	0	0	0	0
Age 7-12 Years				
1	4 (13.8)	3 (10.7)	2 (7.1)	1 (3.6)
2	2 (6.9)	1 (3.6)	3 (10.7)	5 (17.9)
3	5 (17.2)	6 (21.4)	5 (17.9)	4 (14.3)
4	1 (3.4)	1 (3.6)	1 (3.6)	1 (3.6)
5	0	0	0	0
Age >12 Years				
1	0	1 (3.6)	0	0
2	2 (6.9)	2 (7.1)	5 (17.9)	5 (17.9)
3	4 (13.8)	5 (17.9)	4 (14.3)	3 (10.7)
4	6 (20.7)	4 (14.3)	3 (10.7)	3 (10.7)
5	0	0	0	1 (3.6)
All Ages				
1	6 (20.7)	5 (17.9)	3 (10.7)	2 (7.1)
2	4 (13.8)	4 (14.3)	9 (32.1)	11 (39.3)
3	10 (34.5)	11 (39.3)	9 (32.1)	7 (25.0)
4	9 (31.0)	8 (28.6)	7 (25.0)	7 (25.0)
5	0	0	0	1 (3.6)

Note: NCP-3B = Naive CP-CML (Cohort 3b) PFOS
Source: Score Legend: 1=super bad; 2=bad; 3=maybe good or maybe bad; 4=good; 5=super good

Table 10: Summary Statistics for Palatability Assessments - Cohort 3b (study CA180226)

	NCP-3B N=33
First Assessment	
N	29
MEAN	2.8
MEDIAN	3.0
MIN, MAX	1, 4
STANDARD DEVIATION	1.12
Second Assessment	
N	28
MEAN	2.8
MEDIAN	3.0
MIN, MAX	1, 4
STANDARD DEVIATION	1.07
Third Assessment	
N	28
MEAN	2.7
MEDIAN	3.0
MIN, MAX	1, 4
STANDARD DEVIATION	0.98
Fourth Assessment	
N	28
MEAN	2.8
MEDIAN	3.0
MIN, MAX	1, 5
STANDARD DEVIATION	1.03

Note: NCP-3B = Naive CP-CML (Cohort 3b) PFOS
Score Legend: 1=super bad; 2=bad; 3=maybe good or maybe bad; 4=good; 5=super good

For assessment by paediatric subjects, the score of 4 (good) was most frequently reported within the > 12 year age group. The median palatability assessment score each week was 3.0 (maybe good or maybe bad).

Distribution

In study CA180018 cerebrospinal fluid (CSF) PK data were available for 9 subjects. The mean 4 hour post-dose CSF concentration of dasatinib in children and adolescents ranged from 1.0 to 3.8 ng/mL whereas the mean dasatinib plasma concentrations at the same time point ranged from 38 to 88 ng/mL in the same groups of subjects. Hence, in pediatric subjects, the concentrations of dasatinib in CSF at 4 hours post-dose are 1% - 5% of the concentration in plasma. In study CA180038 only 1 subject had measurable concentrations in CSF, 2.3 ng/mL 2 hr post-dose on Day 7.

Elimination

Dasatinib is primarily metabolized by the cytochrome P450 enzyme (CYP) 3A4. Extensive study on the ontogeny of CYP3A4 has showed that the enzyme activity is low at birth and reaches adult values in the first years of life. One subject in the infant and toddler group was included in the analysis.

The dasatinib metabolite, BMS-582691, was measured in study CA180018 and CA18038. It was rapidly formed in paediatric subjects, with the median T_{max} ranging from 0.9 to 2.1 hours.

A summary of the metabolite BMS-582691 PK by dose from study CA180038 is provided in **Table 11**.

Table 11: Summary Statistics of BMS-582691 Pharmacokinetics by Dose in Paediatric Subjects (CA180038)

Dose	N	Cmax (ng/mL) Geomean (CV%)	AUC(0-T) (ng.h/mL) Geomean (CV%)	Tmax (h) Med (min, max)
50 mg/m^2 BID	4	2.8 (84)	11.4 (91)	1.3 (1.0, 24.0)
65 mg/m^2 BID	4	4.6 (58)	17.7 (83)	1.3 (1.0, 2.0)
85 mg/m^2 BID	6	4.4 (35)	25.1 (82)	4.1 (1.0, 4.0)
110 mg/m^2 BID	5	6.9 (82)	21.2 (64)	1.5 (0.5, 6.0)

Dose proportionality and time dependencies

Oral administration of dasatinib to pediatric subjects resulted in systemic exposures in terms of C_{max}, $AUC_{(0-T)}$, and $AUC_{(INF)}$ that were consistent with dose proportionality in the dose range of 60 to 120 mg/m^2. There was an increase (in log scale) in PK parameters with increasing dose as shown by a slope that was significantly different from 0 using the power models for each parameter **(Table 12)**.

The PPK analysis showed that dasatinib concentration time profiles in pediatric subjects can be adequately described by a linear 2-compartment model, which further supports the dose proportionality of dasatinib PK in the pediatric population.

Table 12: Effect of Dose Level Adjusted for Age Group (CA180018)

	Slope	P value[a]	90% Confidence Interval
Cmax (ng/mL)	0.8866	0.0366	0.2005 - 1.5727
AUC(0-T) (ng•h/mL)	1.0735	0.0121	0.3961 - 1.7509
AUC(INF) (ng•h/mL)	1.2843	0.0054	0.5764 - 1.9922

[a] Testing that slope does not equal 0

AUC(0-T) - area under the concentration-time curve from time zero to the time of the last quantifiable concentration, AUC(INF) - area under the plasma concentration-time curve from time zero extrapolated to infinite time Cmax - maximum observed plasma concentration

Influence of Age

In post hoc analyses, there was no statistical evidence of a difference in geometric means of dasatinib Cmax, AUC(0-T) and AUC(INF) between children and adolescents at the different dose levels **(Table 13)**.

Table 13: Differences in PK Parameters Between Age Groups Adjusted for Dose Levels (CA180018)

	P value	Geometric Mean Children	Geometric Mean Adolescents	Ratio of Geometric Mean[a]	90% Confidence Interval
Cmax (ng/mL)	0.845	134.020	139.358	1.040	0.745 - 1.451
AUC(0-T) (ng•h/mL)	0.336	434.412	533.860	1.229	0.860 - 1.755
AUC(INF) (ng•h/mL)	0.3075	475.412	609.560	1.282	0.855 - 1.923

[a] Adolescents/children

AUC(0-T) - area under the concentration-time curve from time zero to the time of the last quantifiable concentration, AUC(INF) - area under the plasma concentration-time curve from time zero extrapolated to infinite time Cmax - maximum observed plasma concentration, PK - pharmacokinetics

Dasatinib has a half-life of 2 – 5 hours also in paediatric subjects.

Special populations

N/A

Pharmacokinetic interaction studies

No pharmacokinetic interaction studies in paediatric patients have been submitted.

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Mechanism of action

N/A

Primary and Secondary pharmacology

Dose-response/Exposure-response analysis of efficacy

With the lower bioavailability of the PFOS to that of the tablet in paediatric subjects, it was important to explore the relationship between efficacy and dasatinib treatment cohort (72 mg/m^2 PFOS vs. 60 mg/m^2 tablet) in order to inform the benefit-risk assessment for the PFOS.

D-R/E-R analyses were performed with respect to two efficacy endpoints in paediatrics subjects with newly diagnosed CML-CP: time to MMR and BCR-ABL pharmacodynamics, using the PK and efficacy data collected in the Phase 2 paediatric study CA180226.

The primary endpoint CCyR was not included as only few subjects were non-responders (n=6).

The longitudinal temporal profiles of BCR-ABL transcript levels in bone marrow cells were evaluated as a complement to the analyses of the dichotomous endpoints of MMR.

D-R efficacy analyses included paediatric subjects with newly diagnosed CML-CP in CA180226 Cohorts 3a and 3b, and the E-R analysis used data only from Cohort 3b. There were 84 subjects treated with dasatinib, 51 (60.71%) of which received dasatinib tablet of 60 mg/m^2 QD, and the rest (n=33) received dasatinib PFOS of 72 mg/m^2 QD.

Analysis of MMR

The relationship was described by a semi-parametric CPH model. The CPH models were developed in 2 stages. First, the relationship between dasatinib treatment cohort (PFOS 72 mg/m^2 vs. tablet 60 mg/m^2) and time to MMR was characterized in a base CPH model. Second, a full model was developed by incorporating effects of pre-specified variables (body weight, age and BCR-ABL levels at baseline) in addition to that of dasatinib treatment cohort. Inferences of covariate effects were based on the full model.

The parameter estimates of the full model are listed in **Table 14**.

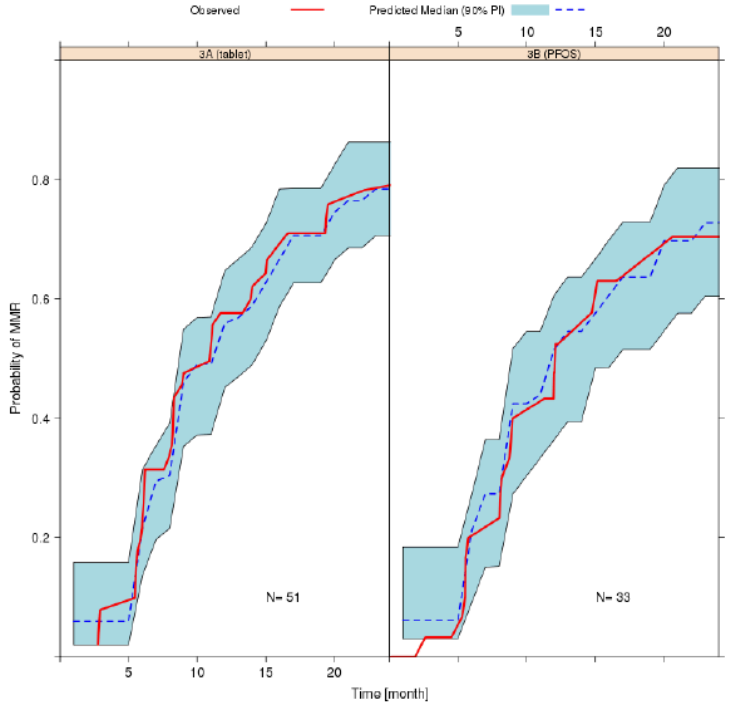
Table 14: Parameter Estimates of E-R (MMR) Full Model

Predictor	Estimate	SE	RSE%	Hazard Ratio Coefficient [a] (95% CI)
Cohort (72 mg/m^2 PFOS vs 60 mg/m^2 tablet)	-0.2371	0.3058	129	0.7889 (0.4332, 1.437)
Age	-0.0482	0.04537	94.12	0.9529 (0.8719, 1.042)
Body Weight	0.0249	0.009821	39.43	1.025 (1.006, 1.045)
Baseline BCR-ABL	-1.464	0.4233	28.91	0.2313 (0.1009, 0.5302)

[a] increase in hazard for every unit increase in continuous predictor variables
Analysis Directory: /global/pkms/CA/180/PFOS-dose-selection/prd/er-mmr/final

The performance of full model was evaluated by comparing the model-predicted cumulative probability of MMR with that determined by Kaplan-Meier analyses. **Figure 2** presents the evaluation results with respect to formulation, the main predictor of interest. The Kaplan-Meier curves were in good agreement with the CPH model predictions, indicating an adequate model performance in cohorts with both tablet and PFOS formulations.

Figure 2: Predictive check of D-R (MMR) full model



Analysis of BCR-ABL

The longitudinal temporal profiles of BCR-ABL transcript levels in bone marrow cells were evaluated to examine patients' response at a better resolution.

The D-R relationship was characterized by a non-linear mixed effect model. First, the parameters that characterized the BCR-ABL time profiles were estimated in the base model. Second, a full model was developed by incorporating effects of all potentially predictive variables (dasatinib treatment cohort, baseline age and body weight) on the dynamics parameters. Inference of covariate effects was based on the full model.

BCR-ABL pharmacodynamics were described by a bi-phasic exponential function with respect to time. The analysis indicated that the decline rate was slightly slower in the PFOS cohort (by ~7%), however, the difference was not statistically significant (95 % CI 0.72 – 1.2).

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics data have been collected in 3 clinical studies in paediatric subjects, 2 phase 1 studies, CA180018 and CA180038, and 1 phase 2 study, CA 180226, cohort 3b. Included paediatric subjects were mainly the target paediatric population, Ph+ CML-CP. PK in paediatric subjects has also been evaluated by PPK analysis.

The pharmacokinetics of dasatinib have been evaluated in 104 paediatric patients in the age 1 to 18 years have been collected -which is adequate to characterize the PK in this population- with leukaemia or solid tumours (72 who received the tablet formulation and 32 who received the powder for oral suspension).

Pharmacokinetics of the tablet formulation of dasatinib were evaluated for 72 paediatric patients with relapsed or refractory leukaemia or solid tumours at oral doses ranging from 60 to 120 mg/m^2 once daily and 50 to 110 mg/m^2 twice daily. Data was pooled across two studies and showed that dasatinib

was rapidly absorbed. Mean T_{max} was observed between 0.5 and 6 hours and mean half-life ranged from 2 to 5 hours across all dose levels and age groups. Dasatinib PK showed dose proportionality with a dose-related increase in exposure observed in paediatric patients. There was no significant difference of dasatinib PK between children and adolescents. The geometric means of dose-normalized dasatinib C_{max}, AUC (0-T), and AUC (INF) appeared to be similar between children and adolescents at different dose levels. A PPK model-based simulation predicted that the body weight tiered dosing recommendation described for the tablet, in section 4.2, is expected to provide similar exposure to a tablet dose of 60 mg/m^2. These data should be considered if patients are to switch from tablets to powder for oral suspension or vice versa.

The PK characteristics of dasatinib appear to be similar in paediatric and adult subjects, and also in the three investigated paediatric age groups, infant/toddlers, children and adolescents. Data are limited in children below the age of 2 years and/or < 10 kg, but suggest a lower exposure for the youngest children.

With no evidence of impact on efficacy for the lower exposure, it is acceptable not to recommend a higher dose in the youngest children. No effect of disease type has been identified. Clearance and volume of distribution increase with increase in weight, supporting the BSA-based dosing in paediatric subjects. Inter-subject variability was considerable in children (48.4 %), but similar to that in adults (44.4 %)**.** Dasatinib was measured in CSF 4 hours post dose with a ratio of 1- 5 %. Data are limited, but dasatinib distribution to CNS appears to be higher in children than in adults.

PPK analysis has showed similar exposure (C_{avgss}, C_{minss}, C_{maxss}) between the 60 mg/m^2 dose of the tablets in paediatric subjects and the adult dose of 100 mg QD. The 60 mg/m^2 tablet dose is considered the reference dose in paediatric subjects.

An age appropriate formulation has been developed for paediatric subjects incapable of/unwilling to swallow tablets. Bioequivalence between the PFOS, dispersed tablets in orange juice and intact tablets has been investigated in a bioequivalence study in healthy adult subjects. The PFOS and the dispersed tablets were not bioequivalent to the reference tablets. In adults, AUC_{inf} was 19 % lower for PFOS and dispersed tablets had a 16 % lower AUC_{inf} compared to intact tablets. This led to a PFOS dose used in cohort 3b in study CA180226 of 72 mg/m^2. PPK model-based simulations assessed exposure of PFOS in paediatric subjects, and this showed an even lower exposure of PFOS in paediatric subjects, namely 40 % lower. A shorter gastric transit time, investigated with a PBPK model, is a plausible explanation for the lower exposure of both PFOS and dispersed tablets. Simulations has predicted a PFOS dose of 90 mg/m^2 to provide similar exposure to the 60 mg/m^2 tablet dose for both C_{avgss}, C_{min} and C_{max}. The proposed paediatric PFOS dose is therefore 90 mg/m^2. The Applicant has suggested a post-marketing PK "window-study" to evaluate the proposed 90 mg/m^2 dose.

Food has an effect on tablet absorption in adults with reduced C_{max} and higher AUC, but with negligible clinical relevance. This also applies to paediatric subjects, when investigated with PBPK simulations.

A weight-tiered approach has been investigated for both PFOS and tablets, and the simulations predict similar exposure to the 60 mg/m^2 dose in paediatric subjects.

The palatability of the PFOS has been assessed to be "fair" in both adult and paediatric subjects with some variability, and the flavour is stable for up to two years after manufacture.

Overall, the pharmacokinetics of dasatinib have been investigated in a substantial number of paediatric subjects, and no major issues has been identified. The use of PPK and PBPK model based simulations to investigate exposure, bioequivalence and food effect in this rare target population is supported. The models have been found to be adequate and suitable for the purposes. The genetic basis and course of Ph+ CML-CP is similar in adult and paediatric patients. A similar exposure-response to dasatinib in

paediatric subjects compared to adults will support extrapolation of adult efficacy data in the proposed indication.

Dose-response and exposure response analysis have been conducted with data from the phase II studyThe CA180226 in 84 paediatric subjects with newly diagnosed (treatment naïve) CML-CP. Dose-response and exposure-response has been explored for two efficacy-endpoints used in CML-CP: MMR and BCR-ABL. Only few patients had dispersed tablets and no effect on D-R or E-R analysis is expected.

No statistically significant relationship was identified between dasatinib dosage form/exposure and efficacy with the dose range of 60 mg/m^2 tablet to 72 mg/m^2 PFOS, however, there was a trend of increased MMR probability and faster decline of BCR-ABL transcript levels with increasing dasatinib exposure measured by C_{avgss}. This support the proposed increase in PFOS dose from 72 mg/m^2 to 90 mg/m^2 to match the exposure of 60 mg/m2 tablets more closely. No change in safety issues can be expected with the proposed higher PFOS dose.

PFOS is proposed indicated to pediatric subjects and adult patients with CML who cannot swallow tablets. Weight tiered doses have been suggested taking into account the lower bioavailability. Pediatric and adults patients > 45 kg are likely to have similar physiology and for patients > 45 kg PFOS dose of 120 mg is proposed in line with the findings in the adult BE study.

Further, it is agreed that the very low bioavailability of dasatinib following suspension administration is not unique to the suspension formulation, but is also observed with the dispersed tablets in adults. Effect of food on the bioavailability and variability of dasatinib for the suspension has not been investigated clinically, but the high intra-subject variability might be related to physiological variability in gastric pH and gastric transit time, administration under fed condition might be preferable as this reduces the variability for the tablets.

The proposed PFOS dose of 90 mg/m^2 is based on simulations, which appear to be justified and acceptable, however, confirmation from clinical data is needed. A PK "window" study has been agreed with a finalized CSR in 1Q 2020. A WT-tiered dosing approach likely to ease daily dosing has been proposed and appears to provide similar exposure with acceptable differences to the tablet reference 60 mg/m^2 to subjects < 45 kg (see RMP).

2.4.5. Conclusions on clinical pharmacology

Overall, the PK data of dasatinib available in paediatric subjects with Ph+ CML-CP adequately support the proposed tablet dose of 60 mg/m^2. An age-appropriate formulation with acceptable taste and taste stability has been developed.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

A post-marketing study to confirm the dasatinib exposure administering 90 mg/m^2 PFOS is recommended.

2.5. Clinical efficacy

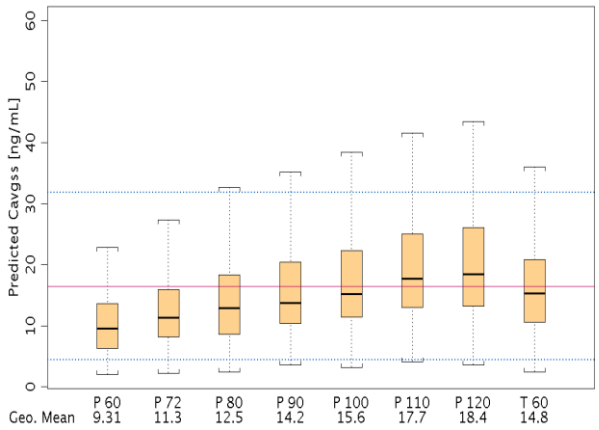
2.5.1. Dose response studies

PPK model-based simulation was used to determine a mg/ m^2 PFOS dose and weight-tiered (WT) doses for both tablet and PFOS, that can provide similar exposure to tablet 60 mg/m^2. The developed full model was used to predict dasatinib exposure in paediatric patients at following BSA-normalized doses:

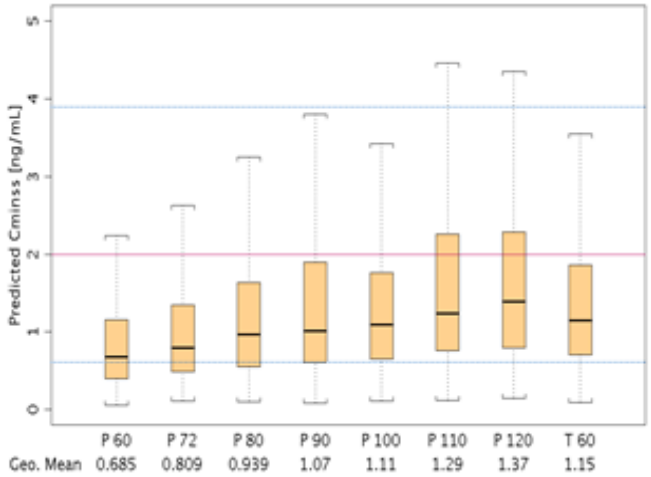
60 mg/m^2 QD given as tablet; 60, 72, 80, 90, 100, 110 and 120 mg/ m^2 QD given as PFOS. The simulation included 500 paediatric subjects and assumed a log-normal body weight distribution as observed in the PPK analysis dataset. **Figure 3** presents distributions of the predicted paediatric C_{avgss}, C_{minss}, and C_{maxss} for the investigated doses of the tablet or PFOS, together with the exposure from the adult dose of the 100 mg QD tablet. C_{minss} is the steady-state trough concentration. Similarly, C_{maxss} and C_{avgss} are the steady-state peak, and time-averaged dasatinib concentrations. The estimated exposure measures were also compared to those in adult subjects treated with dasatinib 100 mg QD as derived from the adult PPK analysis.

Figure 3: Distribution of Model Predicted Dasatinib Steady-State Exposure, by Formulation and Dose

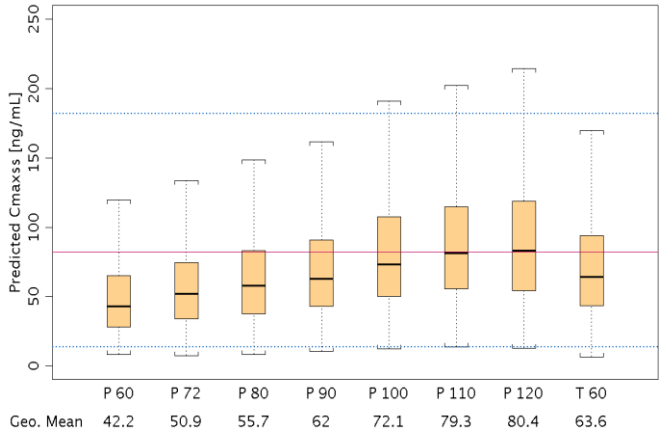
A: Predicted Cavgss



B: Predicted Cminss



C: Predicted Cmaxss



Note: P: PFOS; T: Tablet dose in mg/m^2. The bar inside the box represents the median, edges of the box represent the 25th and 75th percentiles, and whiskers represent the 5th and 95th percentiles. Horizontal lines are the median (solid line) and 5th/95th percentiles (dashed lines) of adult exposure at 100 mg QD.

Tablet – proposed dose 60 mg/m^2

In study CA180018, across the pre-specified dose levels of 60 to 120 mg/ m^2 QD, no maximum tolerated dose (MTD) was identified. These response rates are comparable to those at equivalent adult dosing of 100 mg QD. The efficacy of the 60 and 80 mg/m^2 QD doses were generally comparable; however, the 60 mg/m^2 dose appeared to be better tolerated than the 80 mg/m^2 dose.

Similar exposure to the dasatinib dose of 60 mg/m^2 was achieved in paediatric subjects compared to adult dose of 100 mg QD. The mean observed Cavgss (CV%) value in study CA180018 was 12.79 (59.1%) ng/mL with 60 mg/m^2 QD dasatinib, similar to the mean (CV%) value of 14.16 (20%) ng/mL in adults. Similarly, the mean observed minimum concentration (Cmin) ± SD value was 1.8 ± 1.2 ng/mL at 24 hours post-dose for 60 mg/m^2 QD in paediatric subjects, whereas in adults, the mean steady state Cmin (Cminss) (CV%) value was 2.69 (26%) ng/mL with 100 mg QD. The range of the Cminss values for paediatric and adult subjects overlapped.

Simulation was conducted to predict dasatinib exposure provided by the 60 mg/m^2 tablet in paediatric subjects across their body weight range. It showed that the predicted paediatric exposures (Cavgss, Cminss and Cmaxss) increased slightly with increasing body weight, but generally are consistent with the adult exposures across the body weight range observed in the paediatric clinical studies.

The benefit-risk profile at tablet dose of 60 mg/m^2 was further characterized and confirmed in the Phase 2 study CA180226. The high and durable responses (both cytogenetic and molecular) observed in the study at 60 mg/m^2 tablet are as high as those reported for adult CML-CP treated with dasatinib and for paediatric CML-CP treated with first line imatinib. The safety profile of dasatinib 60 mg/m^2 tablet in CA180226 with paediatric CML-CP subjects was manageable and generally consistent with adult data, except that there were no events of pleural/pericardial effusion, pulmonary oedema / hypertension, or arterial pulmonary hypertension related to dasatinib.

Weight-tiered (WT) dosing - tablets:

WT-tiered dosing in paediatric patients was further evaluated by simulating dasatinib exposures for each body weight tier using the paediatric PPK model (5-120 kg with every 5 kg increment) under various dosing scenarios (tablet dose from 20 to 100 mg), taking into account the available tablet dosing strengths. The WT-tiered doses were selected to produce similar summary steady-state exposures to target exposures of the 60 mg/m^2 tablet QD, which have been demonstrated in study CA180226 to be safe and efficacious in paediatric Ph+ CML-CP patients. The exposures were considered similar if the difference in geometric mean of simulated steady-state exposures are within 20%. Based on the simulations, tablet doses of 40 mg, 60 mg and 70 mg are suggested for paediatric patients weighing from 10 to <20 kg, 20 to <30 kg and 30 to <45 kg, respectively. Paediatric patients weighing at least 45 kg should receive the dose of 100 mg tablet. The tablet formulation is not recommended for patients weighing less than 10 kg, the powder for oral suspension should be use for these patients.

Table 15: Selected Dosage of Dasatinib Tablets for Paediatric Patients with Ph+ CP CML

Body Weight (kg)	Daily Dose (mg)
10 to less than 20 kg	40 mg
20 to less than 30 kg	60 mg
30 to less than 45 kg	70 mg
at least 45 kg	100 mg

PFOS – proposed dose 90 mg/m^2

Dasatinib PFOS has been developed for use in paediatric patients who cannot swallow tablets. The BE study CA180352 characterized the PK of the PFOS and evaluated the bioequivalence of dasatinib between the PFOS or dispersed tablet and the marketed tablet in healthy adult subjects. Results showed that the PFOS and the dispersed tablet were not bioequivalent to the intact tablet formulation. The exposure (by AUC[INF]) for PFOS was found to be approximately 19% less than intact tablets in healthy adults.

The PPK analysis showed that dasatinib administered as PFOS resulted in ~40% lower bioavailability in paediatric subjects. The exposure of PFOS dose at the studied dose of 72 mg/m^2 was ~30% lower than that of tablet dose at 60 mg/m^2, and the magnitude of difference was similar across the age groups.

The E-R analyses explored the relationship between dasatinib treatment cohort and efficacy of Cohort 3a with 60 mg/m^2 tablet and Cohort 3b with 72 mg/m^2 in the Phase 2 study CA180226. Results showed that time to achieve MMR was numerically longer, and the rate of decline of BCR-ABL was numerically slower in paediatric subjects taking 72 mg/m^2 PFOS relative to those taking 60 mg/m^2 tablet, although the difference was not statistically significant. These results suggested that in order to optimize the benefit-risk profile of PFOS use, it is optimal to recommend a PFOS dose that can match the exposure of the 60 mg/m^2 tablet.

All exposure measures (C_{avgss}, C_{minss} and C_{maxss}) increased with increasing dose of PFOS, in a manner proportional to dose. Among the simulated PFOS doses, the Cavgss produced by doses ≤ 80 mg/m^2 was lower than the reference tablet at 60 mg/m^2. At 90 mg/m^2 and 100 mg/m^2 PFOS, C_{avgss} was similar to the reference values, with less than 10% difference of geometric mean. At higher PFOS doses of 110 and 120 mg/m^2, the C_{avgss} generally exceeded the reference values. A similar trend was observed on the distributions of C_{minss} and C_{maxss}. The C_{minss} produced by 90 and 100 mg/m^2 PFOS were similar to that of the tablet 60 mg/m^2. Compared to the C_{maxss} at tablet 60 mg/m^2, C_{maxss} at 90 mg/m^2 PFOS was similar while that at 100 mg/m^2 PFOS was approximately 15% higher.

These simulation results suggested that among the examined PFOS doses, 90 mg/m^2 provides a similar exposure (<10% difference in geometric mean) to the 60 mg/m^2 tablet across age groups and all 3 exposure measures.

Weight-tiered dosing – PFOS:

PPK model-based simulations were also performed to evaluate and select WT-tiered PFOS doses that can provide similar exposure to the 60 mg/m^2 tablet. The same body weight groups (5-120 kg with every 5 kg increment) and dosing scenarios (PFOS doses 20 to 150 mg) were explored and the same exposure similarity criteria (<20% difference in geometric mean) were used as those used in the WT-tiered tablet dose selection.

Based on the simulations, PFOS doses of 40 mg, 60 mg, 90 mg and 105 mg are recommended for paediatric patients weighing from 5 to <10 kg, 10 to <20 kg, 20 to <30 kg and 30 to <45 kg, respectively. Paediatric patients weighing at least 45 kg are recommended to take the dose of 120 mg PFOS.

Table 16: Selected Dosage of Dasatinib PFOS for Paediatric Patients with Ph+ CP CML (10 mg/ml suspension upon constitution)

Body Weight (kg)	Daily Dose, ml (mg)
5 to less than 10 kg	4ml (40 mg)
10 to less than 20 kg	6 ml (60 mg)
20 to less than 30 kg	9 ml (90 mg)
30 to less than 45 kg	10,5 ml(105 mg)
at least 45 kg	12 ml (120 mg)

As shown in **Table 17** the selected PFOS doses meet the exposure similarity criteria, with < 20% difference of geometric mean from the reference exposure (Cavgss) for all body weight tiers.

Table 17: Comparability of Predicted Dasatinib Exposure at Recommended WT-Tiered Doses to Tablet 60 mg/m^2

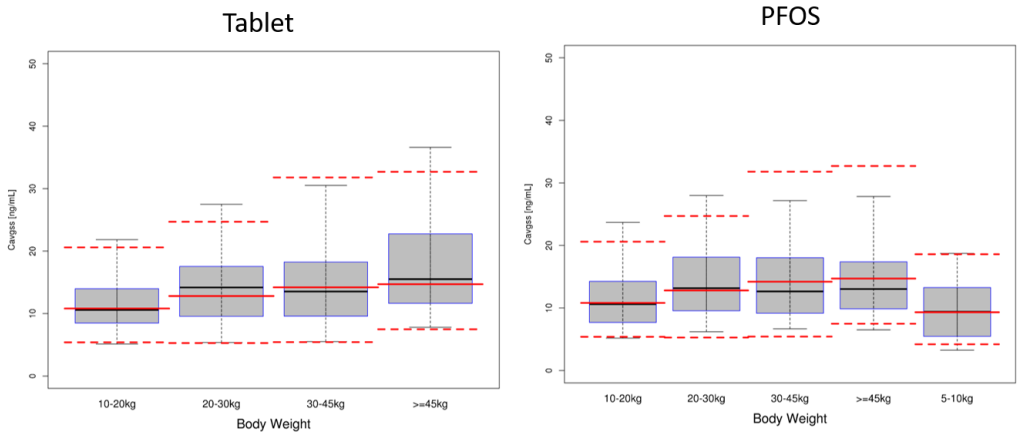
Body Weight [kg]	OnceDaily Dose [mg]	Formulation	% Difference in Geo. Mean		
			Cavgss	Cminss	Cmaxss
5 - < 10[a]	40	PFOS	-2.67	-11.2	28.54
10 - < 20	40	tablet	2.86	2.70	3.29
	60	PFOS	1.90	-6.31	25.39
20 - < 30	60	tablet	8.33	8.04	8.37
	90	PFOS	9.17	0.00	40.11
30 - < 45	70	tablet	-3.62	-3.23	-3.63
	105	PFOS	-6.52	-20.89	23.36
≥ 45	100	tablet	8.00	7.94	8.08
	120	PFOS	-12.7	-23.1	10.6

[a] Tablet is not recommended for 5 to < 10 kg group. Patients in this body weight group are not likely to swallow the tablet.

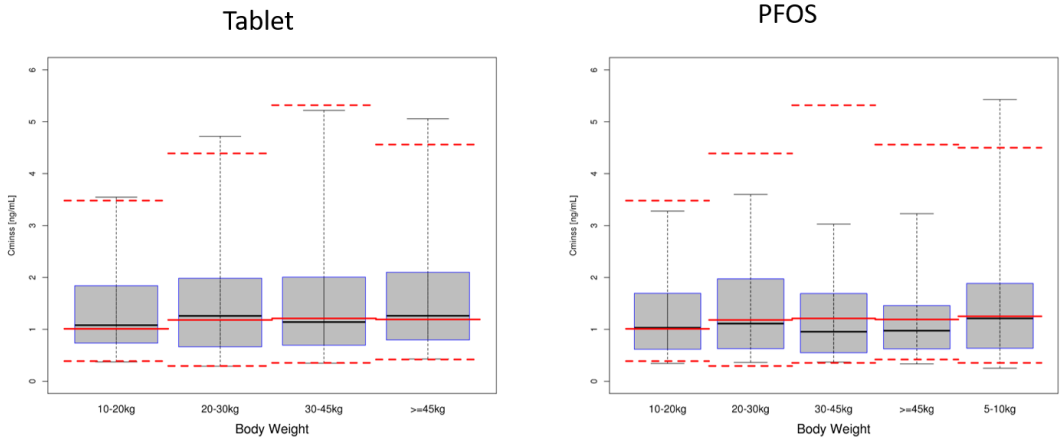
The performance of the selected WT-tiered dosing was further evaluated by plotting the distribution of predicted exposure by body weight in **Figure 4**, and comparing to the predicted reference exposure (median, 5th and 95th percentiles) of the 60 mg/ m^2 tablet for each body weight tier.

Figure 4: Distribution of Dasatinib Exposure at Selected WT-Tiered Doses, by Body Weight Tiers

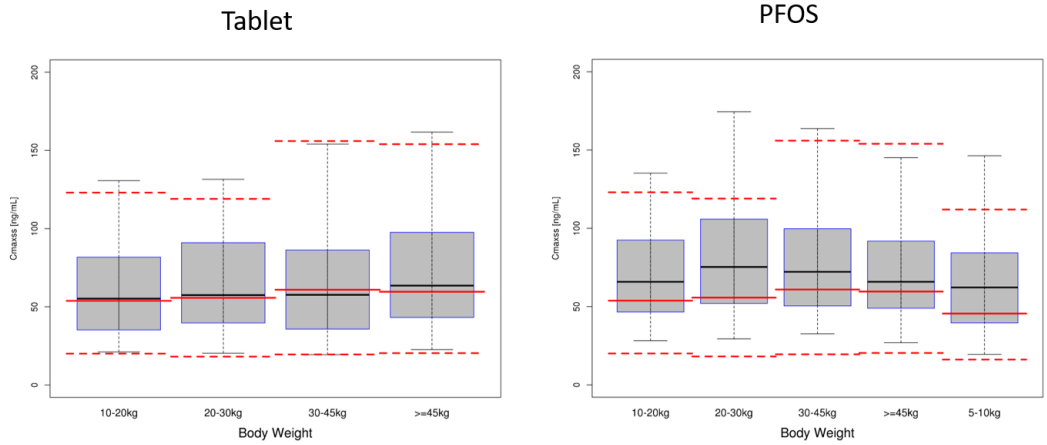
Predicted Cavgss:



Predicted Cminss:



Predicted Cmaxss:



Note: The bar inside the box represents the median, edges of the box represent the 25th and 75th percentiles, and whiskers represent the 5th and 95th percentiles. Horizontal lines are the median and 5th/95th percentiles of exposure at 60 mg/m^2 tablet for each body weight tier.

2.5.2. Main study(ies)

Study CA180226

Methods

Study Participants

Inclusion Criteria

- Life expectancy of at least 12 weeks
- Performance level (Lansky or Karnofsky) at least 50

Subjects were enrolled in the three following cohorts:

Cohort 1: Subjects must have had Ph+ CML in CP which is defined by the presence of all the following criteria:

- < 15% blasts in peripheral blood and bone marrow
- < 20% basophils in peripheral blood
- < 30% blasts + promyelocytes in peripheral blood and bone marrow
- ≥100 X 10^9 platelets/L unless thrombocytopenia secondary to recent treatment
- No extramedullary involvement other than liver and/or spleen
- Ph+ (with 9:22 translocation) must be demonstrated by bone marrow cytogenetics

Cohort 2: Subjects with Ph+ ALL, AP-CML or BP-CML who were resistant or intolerant to, or relapsed after imatinib therapy:

- Ph+ ALL had to be in first or subsequent relapse [defined as loss of a complete hematologic response] or failed to achieve a complete hematological remission.
- Ph+ AP-CML must have met at least one of the following criteria:
    - ≥ 15% but < 30% blasts in peripheral blood or bone marrow
    - ≥ 30% blasts + promyelocytes in peripheral blood and in bone marrow (but percent alone has to be < 30%)
    - ≥ 20% basophils in peripheral blood or bone marrow
    - >100 X 10^9/L platelets unrelated to therapy
- Ph+ BP-CML had to meet either of the following criteria:
    - ≥ 30% blasts in peripheral blood or bone marrow
    - Presence of extramedullary blastic disease other than lymph nodes, liver or spleen

Cohort 3: Subjects must have been newly diagnosed with Ph+ CML in CP which is defined by the presence of all the following criteria (Cohort 3a was administered tablets or tablets for dispersion and Cohort 3b was administered the powder for oral suspension):

- < 15% blasts in peripheral blood and bone marrow
- < 20% basophils in peripheral blood
- < 30% blasts + promyelocytes in peripheral blood and bone marrow
- >100 X 10^9 platelets/L unless thrombocytopenia secondary to recent treatment
- No extramedullary involvement other than liver and/or spleen

- Ph+ (with 9:22 translocation) must have been demonstrated by bone marrow cytogenetics

Subjects in Cohort 1 or Cohort 2 had to be proven resistant or intolerant to imatinib:

- Intolerance Definition: Cohort 1 and Cohort 2, intolerance to imatinib is defined as the occurrence of any toxicity grade ≥ 3 considered at least possibly related to imatinib and that led to discontinuation of previous imatinib therapy.

For Cohort 1, resistance to imatinib must have met at least one of the following criteria:

- Failure to achieve, or loss of, CHR after ≥ 3 months of imatinib at a daily dose of 260 mg/m2 or greater. Capping the dose at 400 mg QD in chronic phase CML subjects with a body surface area (BSA) > 1.5 m2 was accepted.
- Failure to achieve MCyR after ≥ 6 months of imatinib therapy at a daily dose of 260 mg/m2 or greater. Capping the dose at 400 mg QD in chronic phase CML subjects with a BSA > 1.5 m2 was accepted;
- Failure to achieve CCyR after ≥ 12 months of imatinib therapy at a daily dose of 260 mg/m2 or greater. Capping the dose at 400 mg QD in chronic phase CML subjects with a BSA > 1.5 m2 was accepted;
- Absolute increase of ≥ 30% of the percentage of Ph+ metaphases, confirmed at 2 - 4 weeks, after prior MCyR to imatinib at a daily dose of 260 mg/m2 or greater. Capping the dose at 400 mg QD in chronic phase CML subjects with a BSA > 1.5 m2 was accepted.

For Cohort 2, resistance to imatinib must have met at least one of the following criteria:

- Failure to achieve CHR while on imatinib after a ≥ 4-week treatment or a ≥ 50% increase in peripheral blood blasts over a 2-week period
- Subjects who achieved a CHR subsequently no longer meet the criteria consistently over a consecutive 2-week period while receiving imatinib
- Absolute increase of ≥ 30% of the percentage of Ph+ metaphases, confirmed at ≥ 6 week interval, after prior MCyR to imatinib.
- For subjects with Ph+ ALL, first or subsequent relapse [≥ 25% bone marrow blasts] or failure to achieve remission after prior imatinib exposure.

Exclusion Criteria

- Potentially-curative therapy is immediately available, including haematopoietic stem-cell transplantation (HSCT)
- Symptomatic involvement of the central nervous system (CNS), except if signs and symptoms are from isolated leptomeningeal disease
- Isolated extramedullary disease (less than 5% blasts in bone marrow)

Treatments

Dasatinib was administered orally on a once daily schedule. Tablets of 5, 20, and 50 mg or dasatinib PFOS (Oral Suspension constituted with water) was supplied. The investigator (or assigned designee, i.e. study pharmacist) dispensed the proper number of each strength tablet or constituted suspension to the subject or the subject's caregiver to satisfy dosing requirements until the subject's next drug dispensing visit. Individual doses were rounded to the nearest 5 mg (ie up or down). Dose was re-calculated based on BSA every 12 weeks, or more often if necessary.

Objectives

The primary study objectives were cohort specific:

- To estimate the major cytogenetic response (MCyR) rate to dasatinib therapy in children and adolescents with CML-CP who proved resistant to or intolerant to imatinib, representing Cohort 1, specifically: the rate of MCyR as defined as complete (0%) or partial (1-35% of Ph+ metaphases in at least 20 metaphases in bone marrow.
- To estimate the CHR rate in children and adolescents with Ph+ ALL, AP-CML and BP CML, who were resistant to, intolerant to, or who relapsed after prior imatinib therapy, representing Cohort 2, specifically: the rate of CHR including no more than 5% blasts in bone marrow and normal white blood cell count without blasts in peripheral blood.
- To estimate the CCyR rate to dasatinib therapy in children and adolescents with newly diagnosed CP-CMgL who are treatment naïve (except hydroxyurea), representing Cohort 3.

The secondary objectives were:

- To assess the safety and tolerability of dasatinib in children and adolescents treated with dasatinib for relapsed or refractory Ph+ leukaemias.
- To assess the safety and tolerability of dasatinib in children and adolescents with newly diagnosed Ph+ CML-CP who were treatment-naive.
- To evaluate additional measures of efficacy in children and adolescents with newly diagnosed CML-CP or subjects with relapsed or refractory Ph+ leukaemias treated on a given regimen of dasatinib including:
    - Duration and time to MCyR and CHR
    - Progression-free survival, disease-free survival, and overall survival
    - Rates of MCyR, of best cytogenetic response, of CHR and of molecular response (assessed by quantitative PCR)
- To describe the spectrum of the BCR-ABL mutations at baseline, at progression, treatment failure, or end of treatment, and to explore the role of mutations as predictors of response.

The exploratory objectives were:

- To describe growth and development and bone mineral content
- To assess the pharmacokinetics (PK) of dasatinib following oral administration of dasatinib powder for oral suspension (PFOS) in Cohort 3b
- To assess the taste properties of the dasatinib PFOS in the target population.

Outcomes/endpoints

Primary efficacy endpoints were:

- Cohort 1: Major Cytogenetic Response (MCyR) rate, defined as the proportion of all treated subjects who achieved a complete or partial cytogenetic response on study. MCyR is defined as complete (0%) or partial (1%-35% Ph+ metaphases in at least 20 metaphases in bone marrow) cytogenetic response.
- Cohort 2: Complete Hematologic Response (CHR) rate, defined as the proportion of all treated subjects who achieved a confirmed CHR on study. CHR is defined as including no more than 5% blasts in bone marrow and normal white blood cell count without blasts in peripheral blood.

- Cohort 3: Complete Cytogenetic Response (CCyR) rate, defined as the proportion of all treated subjects who achieved a CCyR on study. CCyR rate is defined as 0% Ph+ metaphases in at least 20 metaphases in bone marrow.

Secondary efficacy endpoints were:

- Cohort 1 and Cohort 3: CHR rates
- Cohort 2: MCyR rates
- For all Cohorts:
    - Rates of best cytogenetic response
    - Time to MCyR and duration of MCyR
    - Time to CCyR and duration of CCyR
    - Time to CHR and duration of CHR
    - Progression-free survival (PFS) and disease-free survival (DFS)
    - Overall Survival (OS)
    - Rates of major and complete molecular response
    - The spectrum of the BCR-ABL mutations at baseline, at progression or end of treatment was described and the role of mutations as predictors of response was explored.

Sample size

An exact single-stage design was used to test in each cohort whether dasatinib yielded a response rate that was of clinical interest.

Cohort 1: A response rate in excess of 30% for MCyR was considered of clinical interest. The study design tested the null hypothesis that the true MCyR rate was less than or equal to 30% versus the alternative hypothesis that it exceeded 30%. The one-sided type I error rate was 2.5% and assuming a 60% true MCyR rate (30% more than the response rate under the null hypothesis), 25 response-evaluable subjects were required to have at least 84% power to reject the null hypothesis. The drug was considered of clinical interest if there were 13 or more responders out of the total of 25 response evaluable subjects.

Cohort 2: A response rate in excess of 15% for CHR was considered of clinical interest. The study design tested the null hypothesis that the true CHR rate was less than or equal to 15% versus the alternative hypothesis that it exceeded 15%. The one-sided type I error rate was 2.5% and assuming a 35% true CHR (20% more than the response rate under the null hypothesis), 34 response-evaluable subjects were required to have at least 80% power to reject the null hypothesis. The drug was considered of clinical interest if there were at least 10 responders out of the total of 34 Dasatinib response-evaluable subjects. However, given that enrollment into Cohort 2 was closed early before 34 response evaluable subjects were treated, analyses with respect to that cohort was based on 17 treated subjects. The drug was considered of clinical interest in this cohort if there were at least 7 responders out of 17 response evaluable subjects.

Cohort 3: A response rate in excess of 55% for CCyR was considered of clinical interest. The study design tested the null hypothesis that the true CCyR rate was less than or equal to 55% versus the alternative hypothesis that it exceeded 55%. The one-sided type I error rate was 2.5% and assuming a 75% true CCyR rate among newly diagnosed subjects with CP CML (20% more than the response rate under the null hypothesis), 50 response-evaluable subjects in Cohort 3a yielded 83% power to reject the null hypothesis. The drug was considered of clinical interest if there were 35 or more responders out of the total of 50 response evaluable subjects. A minimum of 30 subjects in Cohort 3b were administered PFOS.

Randomisation

Not applicable.

Blinding (masking)

Not applicable.

Statistical methods

For efficacy analyses, the response rates (hematologic, cytogenetic and molecular) were estimated by cohort (and disease) on all treated subjects along with their two-sided, 95% exact confidence intervals by the method of Clopper and Pearson2.

The following data sets were used in this study:

All treated subjects: All subjects who received at least one dose of dasatinib. Demographic, baseline characteristics, safety and efficacy analyses were performed on all treated subjects.

Mutation data set: All available mutation data from subjects who received dasatinib were included in the mutation data set.

PK data set: All available PK data from subjects in Cohort 3b who received dasatinib PFOS were included in the PK data set.

Results

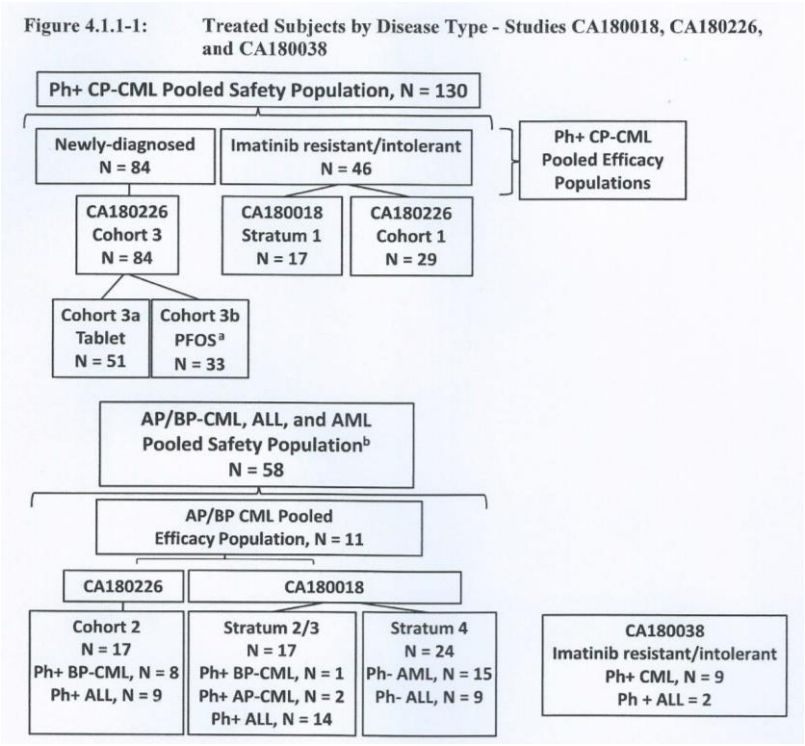
Participant flow

Of the 145 subjects that were enrolled, 130 subjects were treated with dasatinib:

- 29 subjects in Cohort 1: CML-CP
- 17 subjects in Cohort 2: Advanced CML and Ph+ ALL
- 8 subjects with BP-CML
- 9 subjects with Ph+ ALL
- 84 subjects in Cohort 3: Treatment Naive CML-CP
- 51 subjects in Cohort 3a (tablet)
- 33 subjects in Cohort 3b (PFOS)

Of the 130 treated subjects, 50 subjects entered follow-up: 14 subjects in Cohort 1 (48.3%), 13 subjects in Cohort 2 (76.5%), 14 subjects (27.5%) in Cohort 3a, and 9 subjects (27.3%) in Cohort 3b. Of the 50 subjects that entered follow-up, the most common reason for the end of follow-up in Cohort 1 was other (2 subjects [6.9%]) specified as patient transferred to adult unit and bone marrow transplant, Additionally, in Cohort 2 the most common reason for the end of follow-up was death (8 subjects [47.1%]). Finally in Cohort 3a, the most common reason for the end of follow-up was withdrawal by subject (4 subjects [7.8%]).

Figure 5



The median duration of dasatinib therapy in each cohort was as follows: Cohort 1 (49.91 months), Cohort 2 (3.22 months) and Cohort 3 (42.30 months). Within the sub-cohorts of Cohort 3, the median duration of dasatinib therapy in Cohort 3a was 52.24 months, and in Cohort 3b was 27.40 months. As of the data cutoff for this report, a total of 76 subjects (58.5%) were still receiving study drug: 14 subjects (48.3%) in Cohort 1, 1 subject (11.1%) in Cohort 2 (Ph+ ALL), 37 subjects (72.5%) in Cohort 3a, and 24 subjects (72.7%) in 3b. In Cohort 1, the most common reason for study drug discontinuation was progressive disease (5 subjects [17.2%]). In Cohort 2, the most common reasons for study drug discontinuation (7 subjects [41.2%]) were specified as lack of efficacy, increased white cell count, disease and control and start of tyrosine-kinase inhibitor (TKI) and chemotherapy association, loss of response, increase of transcript BCR-ABL in the bone marrow and in blood, and investigator decision. In Cohort 3a, the most common reasons for study drug discontinuation (6 subjects [11.8%]) were specified as T315I mutation, loss of major molecular remission per investigator, loss of CCyR, and subject will undergo to HSCT with a suitable donor found. In Cohort 3b, the most common reasons for study drug discontinuation (6 subjects [18.2%]) were specified as decision to administer HSCT, suboptimal response, 2nd malignancy - emergence of other leukemia type, and subject transitioned to adult hospital.

Recruitment

Subjects were enrolled at 80 sites worldwide in 18 countries: Argentina, Australia, Brazil, Canada, France, Germany, Great Britain, India, Italy, Korea, Mexico, Netherlands, Romania, Russia, Singapore, South Africa, Spain, and USA. The study enrolled subjects sequentially in the 3 Cohorts. The first patient first visit date was 20 March 2009 in Cohort 1, 28 September 2009 in Cohort 2, 19 February 2010 in Cohort 3a and 28 February 2013 in Cohort 3b, respectively. The last patient last visit date for this CSR was 1 September 2016. The clinical database lock for this CSR occurred on 4 November 2016.

Conduct of the study

Changes to the original protocol (dated 09-Jul-2008) up to last subject last visit for this report (01-Sep-2016) include 19 amendments and 8 administrative letters. Most amendments were related to the inclusion of newly-diagnosed patients in December 2009, and three years later for a sub-cohort to receive PFOS. Clarifications on criteria were implemented; removal of information on post-menopausal women and update of information for women of child bearing potential added in amendment 18; amendments reflecting precautions such as hepatitis reactivation, ECG for cardiac monitoring, practical adjustments.

Baseline data

Table 18: Demographics - Studies CA180018 and CA180226 - Subjects with Imatinib-resistant/intolerant CML-CP - All Treated Subjects

	Subjects with Imatinib-resistant/intolerant CML-CP	
	CA180018 Stratum 1 N=17	CA180226 Cohort 1 N=29
Age (years)		
Mean (SD)	12.4 (4.1)	12.60 (4.774)
Median (min-max)	13.0 (4.0-17.0)	13.77 (1.4-20.1)
Age Category (no., %)		
< 2	0	1 (3.4)
≥ 2 to < 7	2 (11.8)	3 (10.3)
≥ 7 to < 12	6 (35.3)	6 (20.7)
≥ 12 to < 18	9 (52.9)	17 (58.6)
≥ 18	0	2 (6.9)
Sex (no., %)		
Male	11 (64.7)	13 (44.8)
Female	6 (35.3)	16 (55.2)
Race (no., %)		
White	16 (94.1)	20 (69.0)
Black or African American	0	2 (6.9)
Asian	1 (5.9)	6 (20.7)
American Indian or Alaska native	0	0
Other	0	1 (3.4)
Ethnicity (no., %)		
Hispanic or Latino	0	2 (6.9)
Not Hispanic or Latino	0	4 (13.8)
Not Reported	17 (100.0)	23 (79.3)
Geographic region (no., %)		
North America	0	5
Europe	17	10
Asia	0	7
Rest of world	0	7

Table 19: Baseline Physical Characteristics, Performance Status, and Extramedullary Disease - Studies CA180018 and CA180226 - Subjects with Imatinib-resistant/intolerant CML-CP - All Treated Subjects

	Subjects with Imatinib-resistant/intolerant CML-CP	
	CA180018 Stratum 1 N=17	CA180226 Cohort 1 N=29
Weight (kg)		
Mean (SD)	47.9 (20.2)	42.9 (19.3)
Median (min-max)	44.8 (17-85)	42.1 (10-74)
Height (cm)		
Mean (SD)	152.7 (23.6)	144.4 (25.9)
Median (min-max)	147.0 (104-185)	153.0 (75-177)

Table 19: Baseline Physical Characteristics, Performance Status, and Extramedullary Disease - Studies CA180018 and CA180226 - Subjects with Imatinib-resistant/intolerant CML-CP - All Treated Subjects

Body surface area (m^2)		
Mean (SD)	1.4 (0.4)	1.30 (0.4)
Median (min-max)	1.4 (0.7-2.0)	1.36 (0.4-1.8)
Performance status: Lansky (%)		
< 60	0	0
60-70	1 (5.9)	0
80-90	1 (5.9)	0
90-100	7 (41.2)	6 (20.7)
Not reported	8 (47.1)	23 (79.3)
Performance status: Karnofsky (%)		
< 60	0	0
60-70	0	0
80-90	1 (5.9)	2 (6.9)
90-100	7 (41.2)	21 (72.4)
Not reported	9 (52.9)	6 (20.7)
Extramedullary involvement (%)		
No	17 (100.0)	25 (86.2)
Yes	0	4 (13.8)
Site of extramedullary involvement:	None reported	
Lymph node, spleen		0
Spleen, visceral liver		3 (10.3)
Spleen, visceral liver, visceral lung		0
Visceral liver		0
Lymph node		0
CNS		0
Spleen		1 (3.4)

Source: CA180018 CSR Table S.3.5 and Table S.3.7, and CA180226 CSR Table S.3.6 and Table S.3.10.

Abbreviations: CNS = central nervous system; SD = standard deviation. Note: Data are as of the primary database lock dates for each study.

Table 20: Demographics - Study CA180226 - All Treated Subjects with Newly Diagnosed Treatment-naive CML-CP

	Cohort 3a (tablet dosing) N=51	Cohort 3b (PFOS dosing) N=33	Cohort 3 (all subjects) N=84
Age (years)			
Mean (SD)	12.28 (4.084)	11.44 (4.912)	11.95 (4.418)
Median (min-max)	12.87 (1.9, 17.8)	11.70 (1.8, 17.5)	12.33 (1.8, 17.8)
Age Category (no., %)			
< 2	1 (2.0)	1 (3.0)	2 (2.4)
≥ 2 to < 7	5 (9.8)	5 (15.2)	10 (11.9)
≥ 7 to < 12	16 (31.4)	12 (36.4)	28 (33.3)
≥ 12 to < 18	29 (56.9)	15 (45.5)	44 (52.4)
Sex (no., %)			
Male	26 (51.0)	19 (57.6)	45 (53.6)
Female	25 (49.0)	14 (42.4)	39 (46.4)
Race (no., %)			
White	31 (60.8)	25 (75.8)	56 (66.7)
Black or African American	3 (5.9)	1 (3.0)	4 (4.8)
Asian	16 (31.4)	7 (21.2)	23 (27.4)
American Indian or Alaska native	1 (2.0)	0	1 (1.2)
Other	0	0	0
Ethnicity (no., %)			
Hispanic or Latino	1 (2.0)	4 (12.1)	5 (6.0)
Not Hispanic or Latino	13 (25.5)	7 (21.2)	20 (23.8)
Not Latino	37 (72.5)	22 (66.7)	59 (70.2)

Table 21: Baseline Physical Characteristics, Performance Status, and Extramedullary Disease - Study CA180226 - All Treated Subjects with Newly Diagnosed Treatment-naive CML-CP

	Cohort 3a (tablet dosing) N=51	Cohort 3b (PFOS dosing) N=33	Cohort 3 (all subjects) N=84
Weight (kg)			
Mean (SD)	41.8 (17.63)	45.5 (26.33)	43.3 (21.39)
Median (min-max)	38.0 (13-91)	38.7 (12-114)	38.4 (12-114)
Height (cm)			
Mean (SD)	148.8 (21.15)	144.6 (28.31)	147.1 (24.14)
Median (min-max)	152.5 (91-182)	149.9 (89-189)	151.5 (89-189)
Body surface area (m^2)			
Mean (SD)	1.30 (0.357)	1.33 (0.503)	1.31 (0.417)
Median (min-max)	1.27 (0.6-2.1)	1.25 (0.5-2.4)	1.27 (0.5-2.4)
Performance status: Lansky (%)			
< 60	0	0	0
60-70	1 (2.0)	1 (3.0)	2 (2.4)
80-90	12 (23.5)	5 (15.2)	17 (20.2)
90-100	10 (19.6)	11 (33.3)	21 (25.0)
Not reported	28 (54.9)	16 (48.5)	44 (52.4)
Performance status: Karnofsky (%)			
< 60	0	0	0
60-70	0	0	0
80-90	11 (21.6)	4 (12.1)	15 (17.9)
90-100	17 (33.3)	12 (36.4)	29 (34.5)
Not reported	23 (45.1)	17 (51.5)	40 (47.6)
Extramedullary involvement (%)			
No	22 (43.1)	15 (45.5)	37 (44.0)
Yes	29 (56.9)	18 (54.5)	47 (56.0)
Site of extramedullary involvement:			
Spleen, visceral liver	11 (21.6)	6 (18.2)	17 (20.2)
Visceral liver	1 (2.0)	0	1 (1.2)
Spleen	17 (33.3)	12 (36.4)	29 (34.5)

Numbers analysed

All treated subjects: 130

Subjects in the Mutation Data Set: 118

Subjects in the PK Data Set: 32

Outcomes and estimation

Table 22: Summary of Efficacy Results - Study CA180226

	Cohort 1 (Non-naive) (N=29)	Cohort 3 (Naive) (N=84)	Cohort 3a (Tablet) (N=51)	Cohort 3b (PFOS) (N=33)
Cytogenetic Assessments				
Cumulative MCyR rate (95% CI):				
At 6 months	79.3% (60.3-92.0)	90.5% (82.1-95.8)	90.2% (78.6-96.7)	90.9% (75.7-98.1)
At 12 months	89.7% (72.6-97.8)	96.4% (89.9-99.3)	98.0% (89.6-100)	93.9% (79.8-99.3)
At any time	89.7% (72.6-97.8)	96.4% (89.9-99.3)	98.0% (89.6-100)	93.9% (79.8-99.3)
Median time to MCyR (95% CI)	3.1 months (2.8-4.1)	3.0 months (2.8-3.0)	3.0 months (2.8-4.3)	2.9 months (2.8-3.1)
K-M estimated MCyR rate	82.6%	96.3%	96.0%	96.8%

Table 22: Summary of Efficacy Results - Study CA180226

	Cohort 1 (Non-naive) (N=29)	Cohort 3 (Naive) (N=84)	Cohort 3a (Tablet) (N=51)	Cohort 3b (PFOS) (N=33)
at 2 years since response (95% CI)	(59.8-93.1)	(88.9-98.8)	(84.9-99.0)	(79.2-99.5)
Cumulative CCyR rate (95% CI):				
At 6 months	65.5% (45.7-	67.9% (56.8-	66.7% (52.1-	69.7% (51.3-
At 12 months	82.1)	77.6)	79.2)	84.4)
At 24 months	75.9% (56.5-	92.9% (85.1-	96.1% (86.5-	87.9% (71.8-
At any time	89.7)	97.3)	99.5)	96.6)
	82.8% (64.2-	94.0% (86.7-	96.1% (86.5-	90.9% (75.7-
	94.2)	98.0)	99.5)	98.1)
	82.8% (64.2-	94.0% (86.7-	96.1% (86.5-	90.9% (75.7-
	94.2)	98.0)	99.5)	98.1)
Median time to CCyR (95% CI)	3.9 months (2.8-5.6)	5.6 months (3.3-5.8)	5.5 months (3.0-5.7)	5.6 months (3.1-6.0)
K-M estimated CCyR rate at 2 years since response (95% CI)	86.2% (62.9-95.4)	98.6% (90.8-99.8)	97.9% (85.8-99.7)	100% (100-100)
Molecular Assessments				
Cumulative MMR rate (95% CI):				
At 6 months	31.0% (15.3-	26.2% (17.2-	31.4% (19.1-	18.2% (7.0-
At 12 months	50.8)	36.9)	45.9)	35.5)
At 24 months	41.4% (23.5-	52.4% (41.2-	56.9% (42.2-	45.5% (28.1-
At any time	61.1)	63.4)	70.7)	63.6)
	55.2% (35.7-	70.2% (59.3-	74.5% (60.4-	63.6% (45.1-
	73.6)	79.7)	85.7)	79.6)
	62.1% (42.3-	79.8% (69.6-	88.2% (76.1-	66.7% (48.2-
	79.3)	87.7)	95.6)	82.0)
Cumulative MR4 rate (95% CI):				
At 6 months	10.3% (2.2-	3.6% (0.7-10.1)	3.9%(0.5-13.5)	3.0% (0.1-15.8)
At 12 months	27.4)	16.7% (9.4-	21.6% (11.3-	9.1% (1.9-24.3)
At 24 months	20.7% (8.0-	26.4)	35.3)	30.3% (15.6-
At any time	39.7)	39.3% (28.8-	45.1% (31.1-	48.7)
	31.0% (15.3-	50.5)	59.7)	36.4% (20.4-
	50.8)	46.4% (35.5-	52.9% (38.5-	54.9)
	34.5% (17.9-	57.6)	67.1)	
	54.3)			
Cumulative CMR rate (95% CI):				
At 6 months	6.9% (0.8-22.8)	1.2% (0.0-6.5)	0% (0-7.0)	3.0% (0.1-15.8)
At 12 months	6.9% (0.8-22.8)	8.3% (3.4-16.4)	9.8% (3.3-21.4)	6.1% (0.7-20.2)
At 24 months	17.2% (5.8-	21.4% (13.2-	29.4% (17.5-	9.1% (1.9-24.3)
At any time	35.8)	31.7)	43.8)	9.1% (1.9-24.3)
	24.1% (10.3-	29.8% (20.3-	43.1% (29.3-	
	43.5)	40.7)	57.8)	
Hematologic Assessments				
Cumulative CHR rate at any time (95% CI):				
Confirmed	93.1% (77.2-	96.4% (89.9-	100% (93.0-	90.9% (75.7-
Unconfirmed	99.2)	99.3)	100)	98.1)
	100% (88.1-	97.6% (91.7-	100% (93.0-	93.9% (79.8-
	100)	99.7)	100)	99.3)

Primary outcome

Cytogenetic Response - Cohort 1

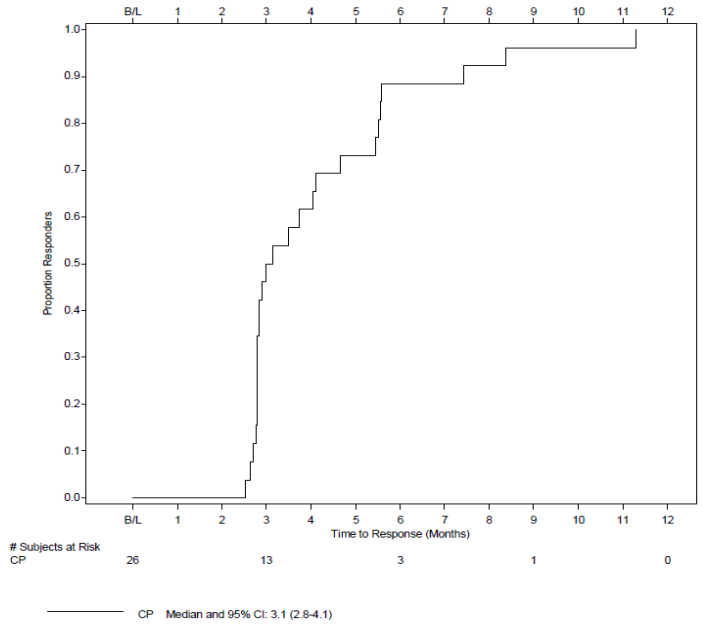
The MCyR rate at any time (Cohort 1 primary endpoint) among the 29 subjects with imatinib-resistant/intolerant Ph+ CML-CP was 89.7% (72.6, 97.8) (Table 7.1-1, Table S.5.14).

- The MCyR rate of clinical interest as defined per protocol (> 30%) was met by 3 months of treatment: 55.2% (95% CI: 35.7, 73.6) (Table S.5.10).
- MCyR rate was 79.3% at 6 months, 89.7% at 12 months, and 89.7% at 24 months of treatment (Table S.5.10).
- CCyR rate was 65.5% at 6 months, 75.9% at 12 months, and 82.8% at 24 months of treatment (Table S.5.12).

The median time to MCyR for subjects who achieved a MCyR was 3.1 months (Table 7.1-1, Figure 7.2.1-1, Table S.5.19). The median time to CCyR for subjects who achieved a CCyR was 3.9 months.

Figure 6

Figure 7.2.1-1: Kaplan-Meier Plot of Time to MCyR - Cohort 1 (Imatinib resistant/intolerant CP-CML) - All Treated Subjects Who Achieved MCyR

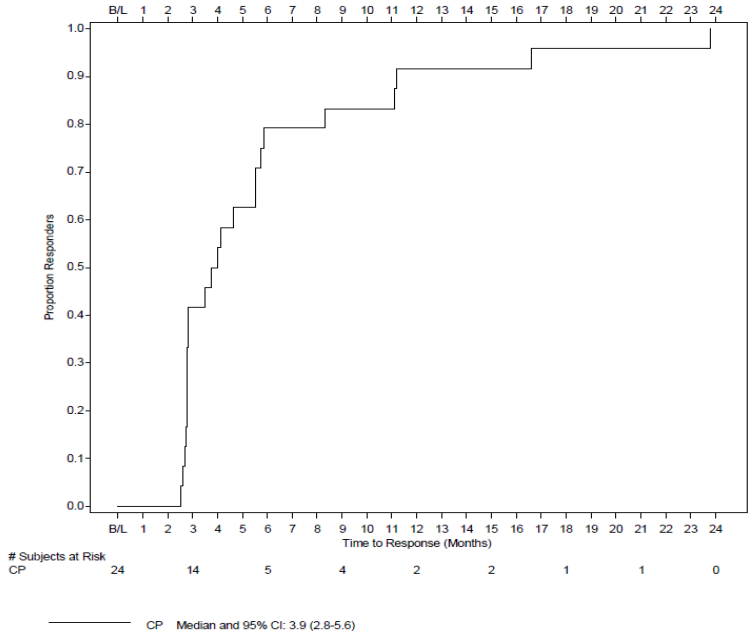


Source: Figure S.5.5

Median durations of MCyR and CCyR were not estimated since less than half of the subjects progressed or died. Progression or death was reported in 5 of 26 subjects with a MCyR and in 4 of 24 subjects with a CCyR.

Figure 7

Figure 7.2.1-2: Kaplan-Meier Plot of Time to CCyR - Cohort 1 (Imatinib resistant/intolerant CP-CML) - All Treated Subjects Who Achieved CCyR



Source: Figure S.5.7

Sensitivity analyses demonstrated that MCyR and CCyR rates were comparable to the response rates when filtered for subjects without relevant protocol inclusion criteria deviations (n = 25), for subjects without major or unknown cytogenetic response at baseline (n = 20), or for subjects without complete or unknown cytogenetic response at baseline (n = 26) . Rates by subject age category also were comparable.

Cytogenetic Response - Cohort 3

CCyR (Cohort 3 primary endpoint) was observed in 94.0% (79/84) of subjects at any time with newly diagnosed Ph+ CML-CP. The MCyR and CCyR rates at 24 months were 96.4% and 94.0%, respectively.

Cohorts 3a and 3b had comparable 24-month rates of MCyR (98.0% and 93.9%) and of CCyR (96.1% and 90.9%), respectively. The CCyR rate of clinical interest as defined per protocol (> 55%) was met at 6 months of treatment in Cohort 3 overall (67.9%, 95% CI 56.8-77.6) and at 9 months of treatment for both Cohort 3a (92.2%, 81.1-97.8) and Cohort 3b (78.8%, 61.1-91.0). Among all Cohort 3 subjects, CCyR rate increased to 94.0% by 15 months of treatment, and MCyR increased from 61.9% at 3 months to 96.4% at 9 months of treatment. For subjects in Cohort 3b who switched dasatinib dosing from PFOS to tablet, cytogenetic response was maintained after the switch.

The median time to MCyR was 3.0 months. Median times to major or complete response were comparable for Cohorts 3a and 3b. Among subjects who achieved CCyR within the first 12 months of treatment (including subjects in Cohort 3b who only received the dasatinib PFOS formulation), the median times to CCyR were 5.5 months for Cohort 3a, 5.6 months for Cohort 3b, and 5.5 months for the entire Cohort 3.

Median durations of CCyR and MCyR were not estimated since less than half of the subjects progressed by the time of database lock. Disease progression was reported in 6 of 81 subjects with a MCyR at any time. Progression was reported in 4 subjects in Cohort 3a out of all 79 subjects in Cohort 3 with a CCyR at any time and by Month 12. No subject in Cohort 3b with a CCyR progressed or died.

Sensitivity analyses demonstrated that MCyR and CCyR rates in Cohort 3 as well as those in Cohorts 3a and 3b were comparable to the response rates when filtered for subjects without relevant protocol inclusion criteria deviations, or for subjects without major, complete, or unknown cytogenetic response at baseline. Rates by subject age category within Cohort 3, Cohort 3a, and Cohort 3b were comparable.

Table 23: Cytogenetic Response Rates at Any Time by Sub-group (Any Number of Metaphases) - Study CA180226 - All Treated Subjects with Newly Diagnosed Treatment-naive CML-CP

	Subjects in category	MCyR Rate		CCyR Rate	
		Subjects (%)	95% CI	Subjects (%)	95% CI
Age category (no., %)					
< 2 years	2	2 (100.0)	15.8-100.0	2 (100.0)	15.8-100.0
≥ 2 to < 7 years	10	10 (100.0)	69.2-100.0	10 (100.0)	69.2-100.0
≥ 7 to < 12 years	28	26 (92.9)	76.5-99.1	25 (89.3)	71.8-97.7
≥ 12 to < 18 years	44	43 (97.7)	88.0-99.9	42 (95.5)	84.5-99.4
≥ 18 years	0	0		0	
Sex (no., %)					
Male	45	45 (100.0)	92.1-100.0	44 (97.8)	88.2-99.9
Female	39	36 (92.3)	79.1-98.4	35 (89.7)	75.8-97.1
Race category (no., %)					
White	56	54 (96.4)	87.7-99.6	53 (94.6)	85.1-98.9
Asian	23	23 (100.0)	85.2-100.0	22 (95.7)	78.1-99.9
Black or African American	4	3 (75.0)	19.4-99.4	3 (75.0)	19.4-99.4
Other	1	1 (100.0)	2.5-100.0	1 (100.0)	2.5-100.0
Geographical region (no., %)					
Europe	20	20 (100.0)	83.2-100.0	20 (100.0)	83.2-100.0
North America	21	19 (90.5)	69.6-98.8	18 (85.7)	63.7-97.0
Asia	21	21 (100.0)	83.9-100.0	20 (95.2)	76.2-99.9
Rest of world	22	21 (95.5)	77.2-99.9	21 (95.5)	77.2-99.9

Source: Summary of Clinical Efficacy Appendix 2 (age), Appendix 3 (sex), Appendix 4 (race), Appendix 5 (geographic region).
Presented are Clopper-Pearson confidence intervals.

Secondary outcome

Hematologic Response - Cohort 1

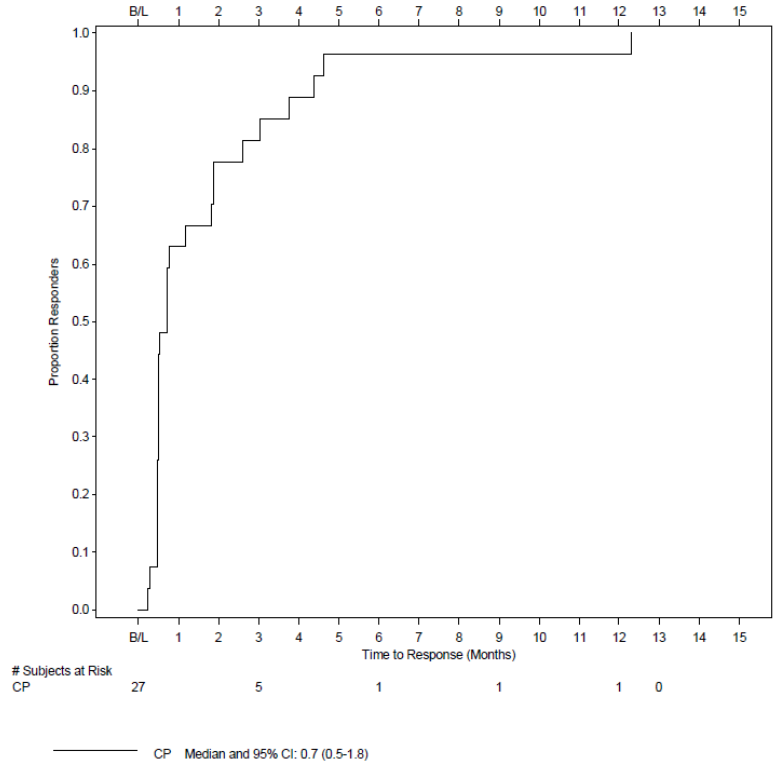
For the 29 subjects with imatinib-resistant/intolerant Ph+ CML-CP in Cohort 1:

- The confirmed CHR rate at 24 months was 93.1% (27/29 subjects).
- By 6 months of treatment, 89.7% (26/29) of subjects achieved a CHR.
- The median time to CHR for subjects with a CHR was 0.7 months
- Median CHR duration was not estimated since less than half of the subjects progressed or died by the time of database lock.
- Loss of response was reported in 5 of 27 subjects with a CHR.
- Disease progression due to loss of CHR occurred in 2 subjects (6.9%).

Sensitivity analyses demonstrated that the CHR rate was comparable to the response rates by subject age category, CHR rate of subjects without relevant protocol inclusion criteria deviations (n = 25), and CHR rate of subjects without CHR or unknown hematologic response at baseline (n = 15).

Figure 8

Figure 7.3.1-1: Kaplan-Meier Plot of Time to Confirmed CHR - Cohort 1 (Imatinib resistant/intolerant CP-CML) - All Treated Subjects who Achieved CHR



Source: Figure S.5.3

Hematologic Response - Cohort 3

For the 84 subjects with newly diagnosed Ph+ CML-CP in Cohort 3:

- The confirmed CHR rate at 24 months was 95.2% (80/84 subjects).

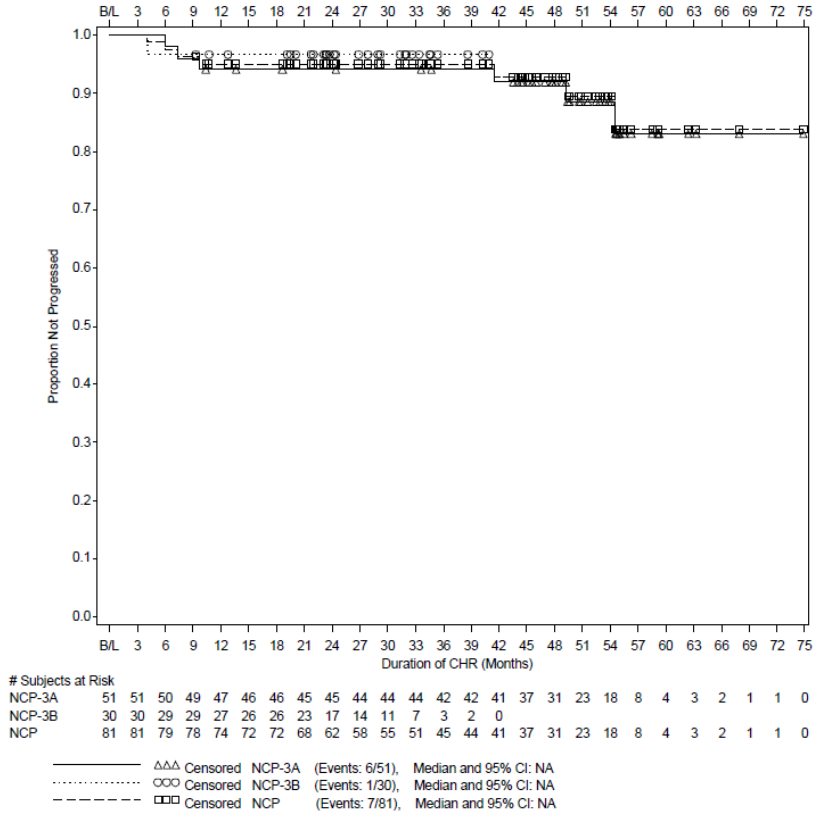
CHR rates at 24 months for Cohorts 3a and 3b were 100% and 87.9%, respectively (Table 7.1-1).

- The Cohort 3 CHR rate at 6 months was 92.9% (78/84 of subjects). Cohorts 3a and 3b had comparable rates over time.
- The median time to CHR for Cohort 3 subjects with a CHR was 1.2 months. Cohorts 3a and 3b had comparable median times to CHR.
- Median CHR duration was not estimated since less than half of the subjects progressed by the time of database lock.
- Loss of response was reported in 7 of 81 subjects with a CHR.
- Disease progression due to loss of CHR occurred only in 2 subjects in Cohort 3a (3.9%).

Sensitivity analyses demonstrated that CHR rates for Cohort 3, Cohort 3a, or Cohort 3b were comparable to the response rates by subject age category (Table S.5.5), CHR rates of subjects without relevant protocol inclusion criteria deviations (n = 81), or CHR rates of subjects without CHR or unknown hematologic response at baseline (n = 82).

Figure 9

Figure 7.3.2-2: Kaplan-Meier Plot of Duration of Confirmed CHR - Cohort 3 (Naive CP-CML) - All Treated Subjects who Achieved CHR



Source: Figure S.5.4

Molecular Response - Cohort 1

The molecular response rates at 24 months in Cohort 1 (n = 29) were 55.2% MMR (16 subjects), 31.0% MR4 (9 subjects), and 17.2% CMR (5 subjects). The molecular response rates at any time were 62.1% MMR (18 subjects), 34.5% MR4 (10 subjects), and 24.1% CMR (7 subjects). MMR was first observed at 3 months of treatment in 5 subjects (17.2%), and this rate rose to 62.1% (18 subjects) at 36 months (Table S.5.31, Figure S.5.17). MR4 was first observed at 3 months of treatment in 1 subjects (3.4%) and this rate rose to 34.5% (10 subjects) at 48 months. CMR was first observed at 6 months of treatment in 2 subjects (6.9%), and this rate rose to 24.1% (7 subjects) at 48 months.

Molecular Response - Cohort 3

For Cohort 3 in total (n = 84), the molecular response rates at 24 months were 70.2% MMR (59 subjects), 39.3% MR4 (33 subjects), and 21.4% CMR (18 subjects) (Table 7.1-1). The molecular response rates at any time for Cohort 3 were 79.8% MMR (67 subjects), 46.4% MR4 (39 subjects), and 29.8% CMR (25 subjects). Since the median exposure duration was 27.40 months in Cohort 3b (see Section 6.1), exposure durations cannot support comparisons of efficacy between Cohorts 3a and 3b beyond 24 months of treatment. Molecular response rates for Cohort 3a and Cohort 3b, respectively, were:

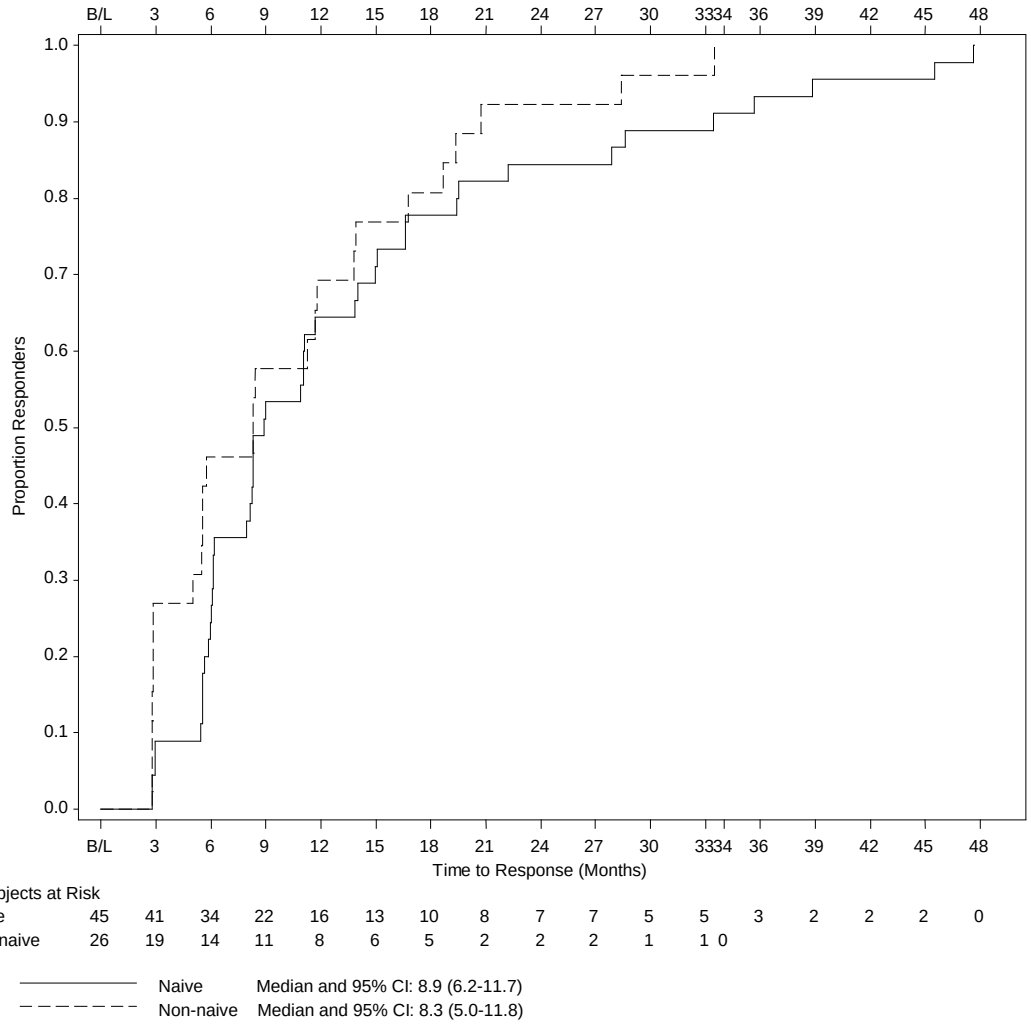
- MMR: 56.9% and 45.5% at 12 months, and 74.5% and 63.6% at 24 months
- MR4: 21.6% and 9.1% at 12 months, and 45.1% and 30.3% at 24 months

- CMR: 9.8% and 6.1% at 12 months, and 29.4% and 9.1% at 24 months

The downward trend in molecular response over time for those subjects in Cohort 3b who switched dasatinib dosing from PFOS to tablet was maintained (Figure S.5.28). The MMR, MR4, and CMR rates at any time, respectively, were 88.2%, 52.9%, and 43.1% in Cohort 3a, and 66.7%, 36.4%, and 9.1% in Cohort 3b (Table S.5.30). The median time to MMR for subjects with a MMR in Cohort 3a, Cohort 3b, and Cohort 3 overall was 8.9 months (Table 7.1-1, Figure 7.4.2-1, Table S.5.34).

For subjects in Cohort 3, Cohort 3a, and Cohort 3b, median durations of MMR were not estimated since less than half of the subjects progressed by the time of database lock. Progression was reported in 3 of 45 subjects with a MMR in Cohort 3a only.

Figure 10: Kaplan-Meier Plot of Time to MMR in Subjects who Achieved MMR - All Treated Subjects with Imatinib-naive and Imatinib-resistant/intolerant CML-CP, *Excluding* Subjects who Received PFOS



Naive: newly diagnosed subjects from Cohort 3A in study CA180226
Non-naive: resistant/intolerant CP-CML subjects from studies CA180018 and CA180226
PFOS: dasatinib administered in powder for oral suspension formulation

Program Source: s:\rho\bms\ca180\clinical\studies\ca180-peds\biostatistics\figures\rg-ef-kmttmmr.sas 24FEB17:11:11:43

Progression-free Survival

PFS was defined in the protocol as time from the first dosing date until the time progressive disease was first documented by the investigator or death. Results based on the alternative definition in which second malignant disease was included as event type besides progressive disease and death, were identical to the results based on the protocol definition. Table 7.5-1 presents the reasons for disease progression among subjects in Cohorts 1 and 3.

Table 24

Table 7.5-1: Summary of Reasons for Disease Progression - Cohorts 1 and 3 - All Treated Subjects

	Number of Subjects (%)			
	Cohort 1 (N=29)	Cohort 3 (N=84)	Cohort 3a (N=51)	Cohort 3b (N=33)
Number of Subjects (%) with Progression	7 (24.1)	7 (8.3)	6 (11.8)	1 (3.0)
Reasons:				
Loss of Major Cytogenetic Response	3 (10.3)	4 (4.8)	4 (7.8)	0
Loss of CHR	2 (6.9)	2 (2.4)	2 (3.9)	0
Development of Blast Phase CML	2 (6.9)	1 (1.2)	0	1 (3.0)

Note: Cohort 1 = imatinib-resistant/intolerant CP-CML; Cohort 3 = naive CP-CML; Cohort 3a = naive CP-CML (tablet); Cohort 3b = Naive CP-CML (PFOS)

Source: Table S.5.36

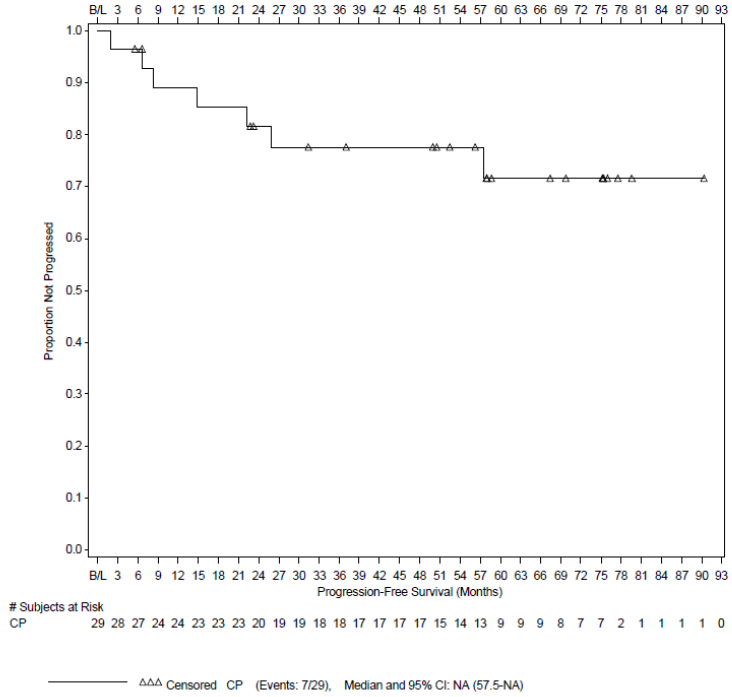
Progression-free Survival - Cohort 1

PFS was defined in the protocol as time from the first dosing date until the time progressive disease was first documented by the investigator or death. Results based on the alternative definition in which second malignant disease was included as event type besides progressive disease and death, were identical to the results based on the protocol definition. The median for protocol-defined PFS was not reached in Cohort 1 since disease progressed in only 7 of 29 subjects. By 24 and 48 months of treatment, an estimated 81.7% and 77.6% of subjects, respectively, in Cohort 1 were alive without disease progression. The 2 subjects with development of BP-CML did not have extramedullary involvement. For Subject CA180226-29-26006, a Grade 3 SAE of progression to blast phase CML (unrelated to study drug) was reported on study Day 59. Dasatinib treatment was discontinued on the same day, and the subject is being treated for this event.

Subject CA180226-92-26058 had bone marrow relapse (lymphoblasts = 20%) detected on Day 678; consequently, dasatinib dose was increased from 100 mg/day to 120 mg/day. On Day 789, the subject was hospitalized for treatment of Grade 3 recurrent leukemia (unrelated to study drug) with 29.6% lymphoblasts in the bone marrow and re-emergence of abnormal karyotype to t(9:22). Following onset of this event, the subject withdrew consent, and dasatinib was discontinued on Day 797. Treatment with cytarabine, daunorubicin, asparaginase, and vincristine was started, and the subject was discharged 24 days after the last dasatinib dose. A cerebral aspergillosis infection was detected 45 days after the last dasatinib dose, and the subject died of respiratory arrest 6 weeks later.

Figure 11

Figure 7.5.1-1: Kaplan-Meier Plot for Progression-free Survival - Cohort 1 (Imatinib resistant/intolerant CP-CML) - All Treated Subjects



Event types: progressive disease and death due to any cause.

Source: Figure S.5.22

Progression-free Survival - Cohort 3

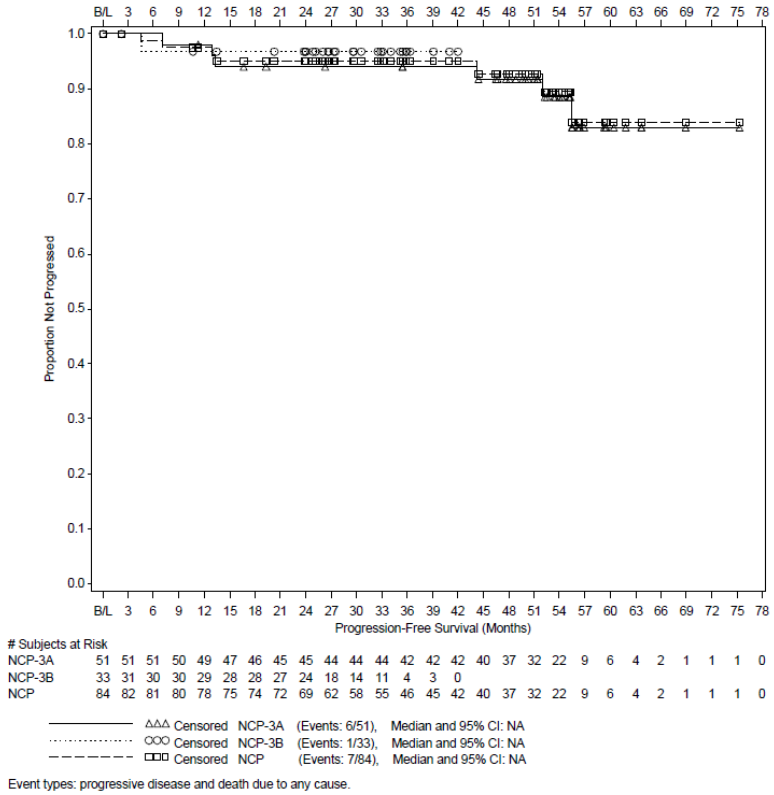
When PFS was based on the alternative definition in which second malignant disease was included as event type besides progressive disease and death, 1 additional event was identified when compared to PFS based on the protocol definition. The median for protocol-defined PFS according to either definition was not reached in Cohort 3, Cohort 3a, or Cohort 3b since only 7 of 84 (8 of 84 according to the alternative definition) of subjects in Cohort 3 progressed. Figure 7.5.2-1 below is based on the protocol definition of PFS.

At 24 months, an estimated 95.1% (95% CI: 87.4%, 98.1%) of subjects in Cohort 3 were alive without progression (94.0% in Cohort 3a and 96.8% in Cohort 3b) according to the protocol definition of PFS, and an estimated 93.9% (95% CI: 86.0%, 97.4%) of subjects in Cohort 3 were alive without progression (94.0% in Cohort 3a and 93.8% in Cohort 3b) according to the alternative definition of PFS.

The 1 subject in Cohort 3b (CA180226-91-26132) with disease progression due to development of blast-phase CML was discontinued from PFOS dasatinib on study Day 137, hospitalized for treatment of a SAE of Grade 4 recurrent leukemia (not related to study drug) on Day 138, and immediately began treatment with hydroxyurea, imatinib (Day 143), asparaginase, and filgrastim. Bone marrow blast cell counts increased from 1% at baseline to 83% (Day 141) prior to the change in treatment. Blast cell counts decreased to 30% at Day 145 and 0% at Day 149 and at follow-up 2 weeks and 4 weeks later. Extramedullary involvement was not detected while on treatment.

Figure 12

Figure 7.5.2-1: Kaplan-Meier Plot for Progression-free Survival - Cohort 3 (Naive CP-CML) - All Treated Subjects



Event types: progressive disease and death due to any cause.

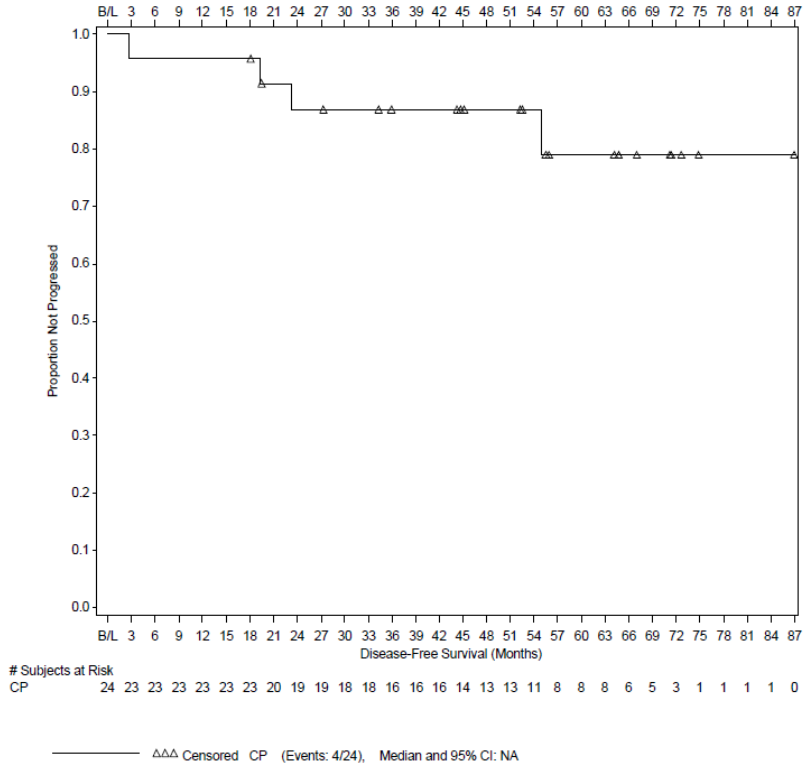
Source: Figure S.5.22

Disease-free Survival –cohort 1

DFS was defined in the protocol for subjects in Cohorts 1 and 3 as time from CCyR until the time progression was first documented by the investigator or death from any cause. Results based on the alternative definition in which second malignant disease was included as event type besides progressive disease and death, were identical to the results based on the protocol definition. The median for protocol-defined DFS was not reached in Cohort 1 since disease was reported in only 4 of 24 subjects with a CCyR. The Kaplan-Meier estimate of DFS at 24 months is 86.9% (95% CI 64.6, 95.6).

Figure 13

Figure 7.6.1-1: Kaplan-Meier Plot for Disease-free Survival - Cohort 1 (Imatinib resistant/intolerant CP-CML) - All Treated Subjects with Complete Cytogenetic Response



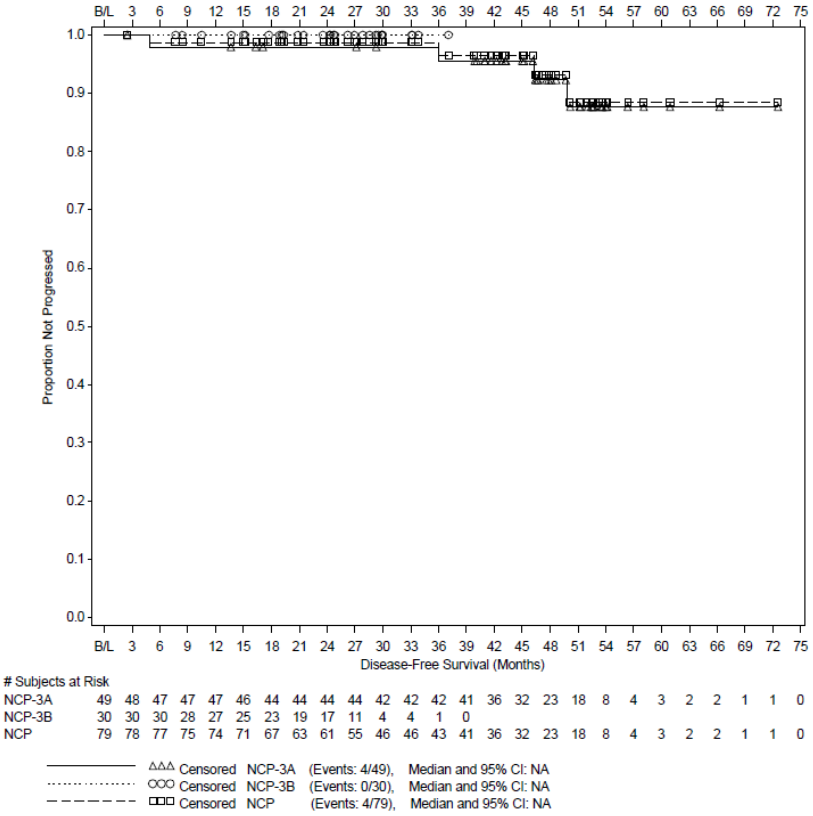
Source: Figure S.5.24

Disease-free Survival - Cohort 3

Results based on the alternative definition in which second malignant disease was included as event type besides progressive disease and death, were identical to the results based on the protocol definition. The median for protocol-defined DFS was not reached in Cohorts 3, 3a, or 3b due to the low rate of disease progression. Disease was reported in 4 of 49 subjects with CCyR in Cohort 3a and in no subjects in Cohort 3b. At 36 months of treatment, an estimated 95.6% (95% CI 83.4, 98.9) of subjects in Cohort 3a with CCyR were alive without disease.

Figure 14

Figure 7.6.2-1: Kaplan-Meier Plot for Disease-free Survival - Cohort 3 (Naive CP-CML) - All Treated Subjects with Complete Cytogenetic Response



Source: Figure S.5.24

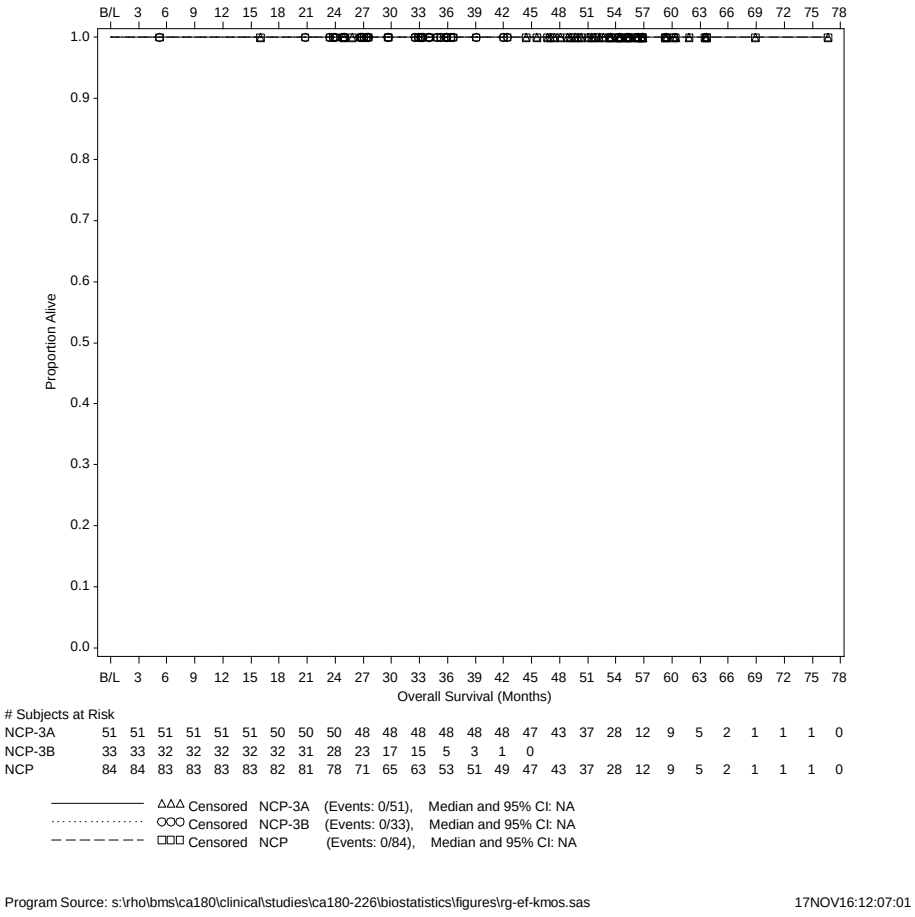
Overall Survival

By the time of database lock (04-Nov-2016), 11 subjects died overall, 10 of whom were in Cohort 2. One subject in Cohort 1 died due to disease progression 1 year after discontinuing treatment. No deaths occurred in Cohort 3.

Since 28 of the 29 subjects in Cohort 1 were still alive, median OS for Cohort 1 had not been reached by the time of database lock.

Figure 15

Figure 5.2-2: Kaplan-Meier Plot for Overall Survival - Study CA180226 - Cohort 3 (Imatinib-resistant/intolerant CML-CP) - All Treated Subjects



BCR-ABL Mutations - Cohort 1

Six subjects in Cohort 1 had single BCR-ABL mutations at baseline. Five of these subjects had a confirmed CHR. Of the 7 subjects with disease progression (see Section 7.5), 4 subjects had mutation data at the time of disease progression, treatment failure, or end of treatment. Of these, 3 subjects had single BCR-ABL mutations. Two of these subjects had these mutations at baseline. No subject had > 1 mutation at baseline or the end of treatment.

BCR-ABL Mutations - Cohort 3

One subject in Cohort 3a had a single BCR-ABL mutation at baseline (P58S), the position of which is located in the Cap region of the ABL protein and N-terminal to the SH3, SH2 and kinase domains.24 The half maximal inhibitory concentration (IC50) to dasatinib for this mutation is unknown. This subject also had a confirmed CHR. Of the 6 subjects in Cohort 3a with disease progression, 2 subjects had mutation data at the time of disease progression, treatment failure, or end of treatment, but neither subject had mutations. No subjects in Cohort 3b with mutation data had BCR-ABL mutations at baseline or at the time of disease progression, treatment failure, or end of treatment, including the 1 subject in Cohort 3b with disease progression.

Ancillary analyses

The efficacy reported with dasatinib 72 mg/m^2 PFOS was compared to historical data with the current standard of care, imatinib, in a comparable paediatric patient population (table x)).

In a French Phase IV study, paediatric subjects with newly diagnosed CML-CP were treated with imatinib 260 mg/m^2. At 12 months, the CCyR rate was 61% (27/44) and the MMR rate was 31% (14/44).

In an Italian study, 39 paediatric subjects with newly diagnosed CML-CP and 8 subjects previously exposed to interferon were treated with imatinib 340 mg/m^2/day. The CCyR rate at 12 months reported, including only evaluable patients was 96% (24/25). The MMR rate at 12 months, including only evaluable patients was 66.6% (14/21) in peripheral blood and 63.7% (14/22) in bone marrow. When accounting for the total number of patients exposed to imatinib, as was done in CA180226 and in the French Phase IV study, the CCyR rate at 12 months was 51% (24/47) and the MMR rate at 12 months was 30% (14/47), which is comparable to the French study and lower than the response rates seen for dasatinib PFOS 72 mg/m^2 based on all the treated patients (N=33), as shown in **Table 25**.

In the imatinib SmPC, in 51 paediatric subjects with newly diagnosed CML-CP, the CCyR rate at 12 months was 65% and MMR was not reported.

Table 25: Efficacy Data of Dasatinib PFOS 72 mg/m^2 Compared to Historical Imatinib Data in Newly Diagnosed Paediatric CML-CP Patients

	Imatinib		Dasatinib PFOS 72 mg/m^2	Dasatinib Tablet 60 mg/m^2
	French Study**Error! Bookmark not defined.**	Italian Study**Error! Bookmark not defined.**	CA180226 Cohort 3b	CA180226 Cohort 3a
CCyR (12 mo) % (# responders/N)	61% (27/44)	51% (24/47)	87.9% (29/33)	96.1% (49/51)
95% CI	-	-	(71.8, 96.6)	(86.5, 99.5)
MMR (12 mo)% (# responders/N)	31% (14/44)	30% (14/47)	45.5% (15/33)	56.9% (29/51)
95% CI	-	-	(28.1, 63.6)	(42.2, 70.7)

Analysis performed across trials (pooled analyses and meta-analysis)

Table 26: Cumulative Rates of Complete Hematologic Response over Time - All Treated AP/BP-CML Subjects from Studies CA180018 and CA180226

	AP/BP-CML N=11
CONFIRMED CHR RATE BY 3 MONTHS	
Rate	3 (27.3)
95% Confidence Interval	(6.0, 61.0)
CONFIRMED CHR RATE BY 6 MONTHS	
Rate	3 (27.3)
95% Confidence Interval	(6.0, 61.0)
CONFIRMED CHR RATE BY 12 MONTHS	
Rate	3 (27.3)
95% Confidence Interval	(6.0, 61.0)
CONFIRMED CHR RATE AT ANY TIME	
Rate	3 (27.3)
95% Confidence Interval	(6.0, 61.0)

Presented are Clopper-Pearson confidence intervals.

No meta-analyses have been performed.

Clinical studies in special populations

The paediatric clinical development program in CML include results obtained in Black/African (4), Caucasian (56), Asian (23) and one American Indian or Alaska native in the main study, newly diagnosed group.

Concomitant morbidities have not been studied.

Supportive studies

Studies CA18003 (Phase 1, dose finding in imatinib intolerant/resistant patients, and solid tumours) and CA18002 (Phase 1, dose escalation in imatinib resistant/intolerant patients) have been discussed under clinical pharmacology.

The cohort 2 in CA180226 with advanced Ph+ leukaemia was closed for further enrolment to monotherapy with dasatinib by DMC due to insufficient treatment response and disease progression.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Three trials supporting this application of Dasatinib for the treatment of children and adolescents aged 1 year to 18 years with Ph+ chronic phase CML are open label, non-comparative trials.

Trial CA180018 was a phase I study in which six patients were treated at 80mg/m^2 QD and eleven patients at 60mg/m^2 QD, with comparable response rates at the two dose levels. Although the rates of Hematologic and Cytogenetic responses were higher in patients treated with the higher dasatinib dose (80 mg/m^2) than with the lower one (60mg/m^2) (while molecular response rates were lower with the higher dose), the conclusion that the dose of 60mg/m2 is the recommended dose for phase II is acceptable, as the number of subjects in each group was very low for these differences to be valued.

Trial CA180226, considered the pivotal study, was a phase II where patients in Cohort 1 (imatinib-resistant/intolerant CML-CP) and Cohort 3 (newly diagnosed treatment-naïve CML-CP, subdivided in Cohorts 3a, with tablet dosing, and 3b, with powder for oral suspension dosing) were treated with dasatinib 60mg/m2 QD.

A third study was presented (Study CA180038), a phase I trial mainly enrolling patients with solid tumor diagnoses, and only 9 patients with CML in non-described phases, who weren't assessed for efficacy with the adequate endpoints for CML. This study is not contributive for the present assessment of efficacy.

Given the low incidence of CML in the paediatric age, and the limited scope of this application for a new formulation in a new indication of a drug that is approved and well-studied in adults in the same indication, as well as the rather objective endpoints of hematologic, cytogenetic, and molecular response rates, the open, non-comparative design of the main trials in the application is acceptable.

Efficacy data and additional analyses

Newly diagnosed patients in the main study on planned daily dasatinib treatment 60mg/m2 tablets (cohort 3a, 51 patients) all achieved CHR at any time, 90% had major cytogenetic response at 6 months, and 98% at 12 months – 67% and 96% being complete, respectively. By molecular biology 31% obtained the classic MMR endpoint at 6 months and 57% at 12 months, 88% at any time on tablet treatment. For newly diagnosed patients in the main study on planned daily PFOS treatment 72mg/m2 (cohort 3b, 33 patients), the same efficacy endpoints were: 91% CHR at any time, 91% had MCyR at 6 months and 94% at 12 months – of these 70% and 88% were complete, respectively. By molecular biology 18% had MMR at 6 months, 46% at 12 months, and 67% at any time.

Other parameters like MR4 and CMR also show less effect by molecular biology in the PFOS group, whereas the time to obtain CCyR is the same (5.5 months). The overall survival for the newly diagnosed patients is identical, whatever the treatment, but it is a major concern that the efficacy by molecular biology is slower and less than on dasatinib tablet treatment. One way to interpret these results are that in a limited group of patients, who do achieve a complete cytogenetic remission and acceptable MMR rates, the risk for disease progression even over more than 5 years of follow up do not necessarily reflect significantly in the results on survival. However, it was demonstrated – as expected from adult CML monitoring – that the progression free survival in landmark plot by *BCR-ABL* less or above 10% at three months in all treated subjects, newly diagnosed treatment naïve patients was significantly less (40%) at 4-5 years in the group with sub-optimal response, versus optimal response patients with a PFS of 90%.

It is acknowledged that the number of paediatric patients is very low, and it is not questioned that the PFOS formulation and administration really fulfil an unmet medical need, which was initiated by a request from CHMP / PDCO some ten years ago. It is convincingly demonstrated that dasatinib treatment has a better effect in CML-CP in children, compared with historic data on imatinib. This is not only due to a PFOS administration *per se*, but the effect of a more potent tyrosine kinase inhibitor (TKI) contributes as well. Clinical data of PFOS supports its use in paediatric CML-CP patients, and the concern of efficacy when compared to tablet formulation in children, and compared to adults may now be reviewed again.

It has been questioned if paediatric CML-CP is the same disease biologically as adult CML-CP. The key pathological factor is the t(9;22), which justifies treatment by the TKI principle, but there seems to be differences in host factors and cell biology translating to another clinical presentation (Hijiya et al. Blood 2016). However, the only rational practice, until further is to treat in the same way as in adult patients, and adhere to the same guidelines from ELN, in Europe (Baccarani et al. Blood 2013). Therefore, when a child is diagnosed with CML-CP the treatment will be evaluated by the recognized response criteria at regular intervals (3,6,12 months in the first year). Accepting the present application and the justification for the dose PFOS 90 mg/m2 in children, the concern of a reduced effect previously, may consequently be anticipated to be corrected by a dose-adjustment if the response is not optimal, as in treatment routinely using the optimal starting dose in adults. Measurement of P-dasatinib is not available in common practice, nor are plasma-measurements of other TKI. Therefore, the monitoring of the young patients is as important to perform, as in adult CML patients, e.g. due to an increasing weight or adverse events, necessitating to consider dose adjustments. The narratives on three patients, who were increased in PFOS dosage, have been noticed and that the treatment apparently was changed in two patients at a relatively late time in the treatment, for which there may be various explanations.

The response assessment using hematologic, cytogenetic and molecular criteria are emphasized together with the recommendation for dose adjustments in the SmPC section 4.2. Naturally, any treatment effect is also a compromise in adverse events and toxicity, which play an important role in

treatment of the individual patient, and with a major importance due to the likely need for chronic treatment and still un-settled risks in this context of young patients. The recommendation in the SmPC: "The following dose escalations shown in Table 2 are recommended in paediatric patients who do not achieve a haematologic or cytogenetic response" is therefore suggested to highlight that the response must be reached at the recommended time points (refer to the product information) and maintained after the first year. The recommendations in dose adjustments for adverse reactions are endorsed. If a dose-increase seems justified due to an unsatisfactory PCR-level, but is not possible to implement due to adverse events, despite measures to try to reduce these manifestations, which may reduce QoL significantly, a change in treatment medication, perhaps mutation analysis has to be considered. The dosing schedule may also contribute to reduce the risk for administration of under-dosing in children, which has been observed in report on medication errors and off-label use from 28-Jun-2015 through 27-June-2017,

It is accepted that the Major Molecular Response rate at 12 months on PFOS is reported to be 45%, which do indicate that 55% of the young patients do not. The MMR, or better is considered a clinical, safe hallmark in adult CML treatment. The MMR Response rate increase after the first year, reflecting the optimal response obtained over time, but also the limbo according to present CML-guidelines, for the patients not in MMR after one year or thereafter – until strict failure may occur. However, the results presented underline the importance of response evaluation in the individual patient, as in adult patients. Any positive immune-modulating effect of dasatinib in children, in tablet or PFOS formulation in children is not clarified, but it may very well add to the long-term effect, because response rates increases over time.

The tablet dose of 60 mg/ m^2 QD for paediatric subjects with CML-CP is supported. It has been sufficiently demonstrated that exposure matches the adult dose of 100 mg QD for the same indication.

The proposed PFOS dose is based on simulations as it was demonstrated that the bioavailability of PFOS compared to tablets in paediatric subjects appeared to be lower in paediatric subjects than in adults. To achieve similar exposure with the PFOS as tablet 60 mg/m^2, the PFOS dose should be 90 mg/m^2. The dosage of 90 mg/m^2 PFOS is justified for children from 1 year of age and day 1 in treatment with dasatinib. (see discussion on clinical pharmacology). However, since no paediatric subjects have been treated with the proposed dose in a clinical setting, methods to ensure close monitoring in the post marketing setting are warranted (see RMP).

In the main study, previously treated, CML-CP patients, the same key-endpoint in imatinib resistant (34 patients) versus intolerant patients (10 patients), showed an unconfirmed CHR rate at any time in all patients (pooled results), and MCyR at six months (79/90%) and at 12 months (85/100%), of these (74/80%) and 77/80%) were complete, respectively. The MMR at 3 months was (15/20%), at 6 months (26/30%) and at 12 months (41/40%). MMR was achieved in 56% and 60%, respectively at any time. The results indicate a more slowly effect in resistant patients, than in imatinib-intolerant, but overall obtained almost the same effect by efficacy parameters in this limited group of patients, but with a trend in particular for resistant patients of less molecular responses. This pattern of results is positive for the effect on previously treated patients as a group, and indicate that dasatinib do overcome imatinib resistance. This pattern of results is somewhat expected compared to the TKI-naïve dasatinib-treated patients as a group.

No point-mutations were demonstrated in six newly diagnosed, tablet treated patients albeit at different time upon disease progression. No subjects in the PFOS treated cohort with mutation data had BCR-ABL mutations at the time of disease progression, treatment failure, or end of treatment, including the 1 subject in Cohort 3b with disease progression. It may indicate that dasatinib do not cause a specific selection pressure in newly diagnosed CML-CP paediatric patients.

The efficacy and survival of patients with Ph+ advanced disease (AP,BP and acute leukaemias) 11 treated subjects (of a total group of 58 patients) in study 180018 and 180226 (all prior imatinib treated) showed an effect of dasatinib treatment, e.g. by 27% CHR at any time, on monotherapy in a group of patients with dubious prognosis. The follow-up time (survival) is very short. No results on effect and safety seem to contra-indicate the use in CP, although observations are confounded by many other factors. Detailed narratives have been provided for seven patients (6 subjects with acute lymphoblastic leukemia [ALL] from either CA180018 or CA180226 [Cohort 2] and 1 chronic myeloid leukemia-blast phase [CML-BP] subject from CA180226 [Cohort 2]) who died of causes other than disease progression. The cause of those 7 deaths were due to expected complications, and the information do not indicate any relation to the dasatinib monotherapy, which however may only be considered a palliative option in these circumstances.

The number of patients in non-white race categories are limited, but is considered acceptable because satisfactory results on efficacy have been reported in adult (east) Asian population.

Nevertheless, it is acknowledged that the number of paediatric patients is in overall very low, however the PFOS formulation and administration will indeed fulfil an unmet medical need, as per a request from CHMP / PDCO.

The results presented, based on patient cohorts, criteria and design of studies on paediatric CML-CP, in imatinib treated or newly diagnosed children, support the applied indication by dasatinib tablet treatment. The introduction of an oral formulation, PFOS into clinical practice is well prepared and very relevant in this age-group.

2.5.4. Conclusions on the clinical efficacy

The results presented based on patient cohorts, criteria and design of studies on paediatric CML-CP, in imatinib treated or newly diagnosed children support the use of dasatinib tablet treatment.

The introduction of an oral formulation, PFOS into clinical practice is very relevant in this age-group. Dosing by tablet and PFOS has been reflected in the SmPC, based on the present knowledge and PPK and PBPK models. The dosage of 90 mg/m^2 PFOS is now satisfactorily justified for the paediatric use of dasatinib.

2.6. Clinical safety

Patient exposure

A total of 188 patients may be included in the review on exposure to dasatinib in paediatric Ph+ leukaemias.

Table 27: Extent of Exposure- All Treated Subjects in the Pooled Population

	Imatinib		Total
AP/BP CML, ALL, and AML N=58	Naive N=84	Resistant/Intolerant N=46	CP CML N=130	Total N=188
Average daily dose (mg/m2/day)[a]				
MEAN (SD)	59.59 (9.849)	63.29 (12.711)	60.90 (11.042)	79.86 (19.248)	66.75 (16.557)
MEDIAN (MIN - MAX)	59.84 (37.2, 98.7)	59.81 (35.1, 100.7)	59.81 (35.1, 100.7)	79.70 (20.4, 125.0)	63.00 (20.4, 125.0)
Duration of therapy (months)				
MEDIAN (MIN - MAX)	42.30 (0.1, 75.2)	38.88 (1.9, 99.6)	42.30 (0.1, 99.6)	1.64 (0.0, 75.0)	26.23 (0.0, 99.6)
N of subjects (%) with <=3	2 (2.4)	3 (6.5)	5 (3.8)	39 (67.2)	44 (23.4)
N of subjects (%) with >3-6	1 (1.2)	3 (6.5)	4 (3.1)	9 (15.5)	13 (6.9)
N of subjects (%) with >6-12	3 (3.6)	6 (13.0)	9 (6.9)	6 (10.3)	15 (8.0)
N of subjects (%) with >12-24	9 (10.7)	4 (8.7)	13 (10.0)	1 (1.7)	14 (7.4)
N of subjects (%) with >24-36	23 (27.4)	7 (15.2)	30 (23.1)	1 (1.7)	31 (16.5)
N of subjects (%) with >36	46 (54.8)	23 (50.0)	69 (53.1)	2 (3.4)	71 (37.8)
Duration of therapy excluding interruptions (months)				
MEDIAN (MIN - MAX)	42.10 (0.1, 73.4)	37.88 (1.9, 99.3)	42.10 (0.1, 99.3)	1.54 (0.0, 75.0)	26.18 (0.0, 99.3)
N of subjects (%) with <=3	2 (2.4)	3 (6.5)	5 (3.8)	42 (72.4)	47 (25.0)
N of subjects (%) with >3-6	1 (1.2)	4 (8.7)	5 (3.8)	8 (13.8)	13 (6.9)
N of subjects (%) with >6-12	4 (4.8)	5 (10.9)	9 (6.9)	4 (6.9)	13 (6.9)
N of subjects (%) with >12-24	8 (9.5)	4 (8.7)	12 (9.2)	1 (1.7)	13 (6.9)
N of subjects (%) with >24-36	23 (27.4)	7 (15.2)	30 (23.1)	1 (1.7)	31 (16.5)
N of subjects (%) with >36	46 (54.8)	23 (50.0)	69 (53.1)	2 (3.4)	71 (37.8)

[a] This includes tablets and powder for oral suspension (PFOS) dasatinib treatment for naive subject in the CML-CP Population

Adverse events

The tabulated Aes in the same population of newly diagnosed, previously treated and patients with advanced disease in monotherapy with dasatinib is presented in **Table 28**.

Table 28

Table 5.1-1: Summary of Safety Results - Pooled Population (CA180018 + CA180226)

	Number (%) of Subjects, Worst CTC Grade									
	Chronic Phase CML									
	Newly-diagnosed N = 84		Imatinib Resist/Intol N = 46		Total CP-CML N = 130		AP/BP CML, ALL, AML N = 58		Total N = 188	
	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4
Deaths	0		4 (8.7)		4 (3.1)		45 (77.6)		49 (26.1)	
All AEs	83 (98.8)	55 (65.5)	44 (95.7)	29 (63.0)	127 (97.7)	84 (64.6)	58 (100.0)	27 (46.6)	185 (98.4)	111 (59.0)
Drug-Related AEs	69 (82.1)	32 (38.1)	41 (89.1)	17 (37.0)	110 (84.6)	49 (37.7)	46 (79.3)	23 (39.7)	156 (83.0)	72 (38.3)
Drug-Related SAEs	8 (9.5)	6 (7.1)	8 (17.4)	7 (15.2)	16 (12.3)	13 (10.0)	19 (32.8)	16 (27.6)	35 (18.6)	29 (15.4)
Drug-Related AEs leading to discont.	1 (1.2)	1 (1.2)	1 (2.2)	0	2 (1.5)	1 (0.8)	2 (3.4)	1 (1.7)	4 (2.1)	2 (1.1)
Drug-related AEs of Special Interest										
Fluid Retention	9 (10.7)	0	4 (8.7)	0	13 (10.0)	0	5 (8.6)	1 (1.7)	18 (9.6)	1 (0.5)
Superficial Edema	6 (7.1)	0	3 (6.5)	0	9 (6.9)	0	2 (3.4)	0	11 (5.9)	0
Pleural Effusion	0	0	0	0	0	0	3 (5.2)	1 (1.7)0	3 (1.6)	1 (0.5)
Generalized Edema	2 (2.4)	0	0	0	2 (1.5)	0	0	0	2 (1.1)	0
CHF/Cardiac Dysfunct.	2 (2.4)	0	1 (2.2)	0	3 (2.3)	0	0	0	3 (1.6)	0
Pulmonary Edema	0	0	0	0	0	0	0	0	0	0
Pulmonary Hypertension	0	0	0	0	0	0	0	0	0	0
Respiratory Disorders	3 (3.6)	0	7 (15.2)	0	10 (7.7)	0	2 (3.4)	0	12 (6.4)	0
Chest pain	1 (1.2)	0	1 (2.2)	0	2 (1.5)	0	0	0	2 (1.1)	0
Shortness of Breath	2 (2.4)	0	3 (6.5)	0	5 (3.8)	0	2 (3.4)	0	7 (3.7)	0
Cardiac Disorders	1 (1.2)	0	1 (2.2)	0	2 (1.5)	0	0	0	2 (1.1)	0
PAH	0	0	0	0	0	0	0	0	0	0
Pediatric Growth/Development	2 (2.4)	0	4 (8.7)	1 (2.2)	6 (4.6)	1 (0.8)	0	0	6 (3.2)	1 (0.5)

Table 5.1-1: Summary of Safety Results - Pooled Population (CA180018 + CA180226)

	Number (%) of Subjects, Worst CTC Grade									
	Chronic Phase CML									
	Newly-diagnosed N = 84		Imatinib Resist/Intol N = 46		Total CP-CML N = 130		AP/BP CML, ALL, AML N = 58		Total N = 188	
Bleeding-related Events (Hemorrhage)	8 (9.5)	1 (1.2)	4 (8.7)	0	12 (9.2)	1 (0.8)	6 (10.3)	4 (6.9)	18 (9.6)	5 (2.7)
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Hematology Laboratory Abnormalities[a]										
No. Subjects Assessed (N)	**83**		**46**		**129**		**54**		**183**	
Leukopenia	10 (12.0)	2 (2.4)	2 (4.3)	0	12 (9.3)	2 (1.6)	6 (11.1)	16 (29.6)	18 (9.8)	18 (9.8)
Neutropenia	19 (22.9)	9 (10.8)	7 (15.2)	6 (13.0)	26 (20.2)	15 (11.6)	10 (18.5)	31 (57.4)	36 (19.7)	46 (25.1)
Thrombocytopenia	8 (9.6)	2 (2.4)	2 (4.3)	2 (4.3)	10 (7.8)	4 (3.1)	10 (18.5)	32 (59.3)	20 (10.9)	36 (19.7)
Anemia	13 (15.7)	5 (6.0)	0	1 (2.2)	13 (10.1)	6 (4.7)	16 (29.6)	6 (11.1)	29 (15.8)	12 (6.6)
Serum Chemistry Abnormalities[a]										
No. Subjects Assessed (N)	**83**		**46**		**129**		**55**		**184**	
ALT (high)	2 (2.4)	0	1 (2.2)	0	3 (2.3)	0	7 (12.7)	2 (3.6)	10 (5.4)	2 (1.1)
AST (high)	0	0	0	0	0	0	6 (11.3)	1 (1.9)	6 (3.3)	1 (0.5)
Total Bilirubin (high)	0	0	2 (4.3)	0	2 (1.6)	0	0	0	2 (1.1)	0
Serum Creatinine (high)	0	0	0	0	0	0	0	0	0	0

Abbreviations: Adv. = advanced; Resist/Intol = resistant/intolerant; discont. = discontinued; dysfunct. = dysfunction; CHF = congestive heart failure; PAH = pulmonary arterial hypertension; ALT = alanine aminotransferase; AST = aspartate aminotransferase; No. = number.

[a] Hematology and Serum Chemistry Abnormalities are based on worst-grade abnormal laboratory values at any time point; refer to Table S.6.15 of the CA180226 CSR for hematology-related and serum chemistry-related abnormalities that were reported as AEs by the investigator.

Source: Table-1 of the SCS[38]

A similar pattern of AEs is observed in newly diagnosed and previously TKI-treated CML-CP patients. Almost all subjects experience AE, and excpet for hematologic AEs manifested by cytopenias most AE are less than grade 3. The two most notably observations is the very positive result that no deaths were recorded in CP patients, and the second is the abscence of pleural effusions, which is a frequent clinical problem in treatment of adult CML. Pediatric patients in the CA180226 trial had an approximately 50% lower Cmin with dasatinib 60 mg/m2 tablet than adult patients with dasatinib 100 mg. Thus, the frequency of events of pleural effusion, ascites, pericardial effusion, pulmonary edema, or pulmonary hypertension were expected to be lower (or absent) in pediatric patients treated with the 60 mg/m2 dose of dasatinib. Moreover, dasatinib-related pleural effusion may occur through a reduction in interstitial fluid pressure or vascular permeability changes, which are more frequent in adults.

Serious adverse event/deaths/other significant events

Symptoms like diarrhoea, rash, headache, oedema and muscle-joint are Present to a similar degree as the AE profile of dasatinib in adults. Some symptoms like diarrhea may be potentially more dangerous in small children than in adults, but still almost always less than grade 3. Some cardiac manifestations have been observed, however not severe and appear manageable. No clinically meaningful cardiac impact on QTc or function seems to have been observed.

Likely, the less concurrent comorbidity at inclusion or follow-up in children compared to adult patients have some influence on the impression of an acceptable AE profile of dasatinib in first- or second line treatment in CML-CP. Bleeding may pose a problem in adults, and have been observed, but none severe. Paediatric growth and development AEs were not observed in dasatinib first line treatment, and observations in previously treated patients may include some late effect of imatinib. Therefore the planned follow-up on all patients is very relevant to settle this AE, which however may improve over time and may be considered acceptable given the indication, and in only 2% considered to be severe. The current protocol language defines the duration of Long-term Growth and Development Assessments in alignment with the RMP and PIP, which is a yearly assessment while on treatment and yearly for up to 5 years after treatment discontinuation. Overall, 23 subjects were enrolled in Cohort 3 (< 11 years old), and currently >50% of those subjects are on treatment after more than 5 years. There is no protocol defined end of Long-term Growth and Development Assessments on treatment. BMS agrees to amend Study CA180226 to require early long-term growth and development assessments for subjects on treatment in Cohort 3 who were < 11 years old when enrolled, continuing until subjects are 18 years old. It is noticed, that overall, 3 subjects in the study received levothyroxine while on treatment with dasatinib.

Liver or renal affection by treatment with dasatinib is not a specific problem in paediatric CML-CP.

Serious adverse events and deaths

SAE

Except for infections and SAEs from blood- and lymphatic system contributing to the majority of SAEs, no special AE has emerged as a major problem. The distribution of SAEs are similar in naïve and TKI-treated CML-CP patients, and a trend towards more grade 3 AEs in imatinib resistant/intolerant patients (35%) than in newly-diagnosed treated by dasatinib (26%) (Table 2.3-1). As expected the symptoms and manifestations are much more extensive in advanced Ph+ leukaemias, but these observations do not distract the favourable impression by dasatinib treatment in CML-CP in children. **(Table 29)**

Table 29

Table 2.3-2: Drug-related SAEs by Worst CTC Grade Reported in ≥ 1% of Treated Subjects- Pooled Population

System Organ Class Preferred Term	Chronic Phase CML					
	Naive N=84		Imatinib Resistant/Intolerant N=46		Total CP CML N=130	
	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)
TOTAL SUBJECTS WITH AN EVENT	8 (9.5)	6 (7.1)	8 (17.4)	7 (15.2)	16 (12.3)	13 (10.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (3.6)	3 (3.6)	3 (6.5)	3 (6.5)	6 (4.6)	6 (4.6)
FEBRILE NEUTROPENIA	1 (1.2)	1 (1.2)	0	0	1 (0.8)	1 (0.8)
ANAEMIA	2 (2.4)	2 (2.4)	1 (2.2)	1 (2.2)	3 (2.3)	3 (2.3)
NEUTROPENIA	0	0	2 (4.3)	2 (4.3)	2 (1.5)	2 (1.5)
GASTROINTESTINAL DISORDERS	1 (1.2)	1 (1.2)	0	0	1 (0.8)	1 (0.8)
HAEMATOCHEZIA	1 (1.2)	1 (1.2)	0	0	1 (0.8)	1 (0.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (1.2)	0	0	0	1 (0.8)	0
OEDEMA PERIPHERAL	1 (1.2)	0	0	0	1 (0.8)	0
INFECTIONS AND INFESTATIONS	1 (1.2)	1 (1.2)	1 (2.2)	1 (2.2)	2 (1.5)	2 (1.5)
INFECTION	0	0	1 (2.2)	1 (2.2)	1 (0.8)	1 (0.8)
PERIORBITAL CELLULITIS	1 (1.2)	1 (1.2)	0	0	1 (0.8)	1 (0.8)
INVESTIGATIONS	1 (1.2)	0	0	0	1 (0.8)	0
WHITE BLOOD CELL COUNT DECREASED	1 (1.2)	0	0	0	1 (0.8)	0
CARDIAC DISORDERS	0	0	2 (4.3)	0	2 (1.5)	0
LEFT VENTRICULAR DYSFUNCTION	0	0	1 (2.2)	0	1 (0.8)	0
PALPITATIONS	0	0	1 (2.2)	0	1 (0.8)	0
IMMUNE SYSTEM DISORDERS	1 (1.2)	1 (1.2)	0	0	1 (0.8)	1 (0.8)
DRUG HYPERSENSITIVITY	1 (1.2)	1 (1.2)	0	0	1 (0.8)	1 (0.8)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (1.2)	0	1 (2.2)	0	2 (1.5)	0
OVERDOSE	1 (1.2)	0	1 (2.2)	0	2 (1.5)	0
HEPATOBILIARY DISORDERS	0	0	1 (2.2)	1 (2.2)	1 (0.8)	1 (0.8)
HEPATIC FUNCTION ABNORMAL	0	0	1 (2.2)	1 (2.2)	1 (0.8)	1 (0.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	1 (2.2)	1 (2.2)	1 (0.8)	1 (0.8)
BONE PAIN	0	0	1 (2.2)	1 (2.2)	1 (0.8)	1 (0.8)

One potentially serious adverse event, which cannot be described until further follow-up is the impact of dasatinib treatment on fertility. Rational measures have been instituted by information to female patients. The risk of developmental defects in a foetus during non-imatinib TKI treatment is not known. It is acknowledged that it is mentioned in the SmPC (section 4.6) that physicians and other healthcare providers should counsel male patients of appropriate age about possible effects of SPRYCEL on fertility, and this counselling may include consideration of semen deposition.

Deaths

In the **CML-CP pooled population**, there were 4 (8.7%) deaths reported in the imatinib resistant/intolerant group, 1 cerebral haemorrhage, 1 disease progression, 2 'other'. For the cases reported as 'other' 1 subject died due to fatal bleeding in digestive tract and the other cause was respiratory failure due to the disease.

There were no deaths within 30 days of last treatment. As of the database lock, none of the 84 naïve subjects have died (Table 2.2-1).

In the **advanced CML, Ph+ ALL and AML pooled population**, 45 subjects died (77.6%). 32 subjects died due to disease progression, 7 due to the reason as 'other', 5 due to infections, and 1 due to fatal bleeding. 17 (29.3%) deaths occurred within 30 days of last treatment, the most common reason being 'other' (Table 2.2-1).

A listing of deaths in all treated subjects is provided in Appendix 16.

Details for deaths occurring in CA180226 are presented in Table S.6.2 of the CA180226 Final CSR and in Table 9.2 of the CA180018 Final CSR. No safety issues on dasatinib emerge.

Long-term Safety-Effects on Growth and Development

The effects of dasatinib on Growth and Development and Bone Metabolism is part of the long term safety assessment, assessed annually while subjects is on study therapy and were to be followed for 5 years from the time the subject discontinued the study therapy.

Dasatinib administered to paediatric subjects appears to have no clinically significant impact as measured by increases or decreases in Z-scores for weight, height, or BMI, and compared to reference ranges during the study. However, it is difficult to make any definitive conclusions from these data, particularly considering chronic disease in these patients may affect these parameters.

In general, a Z-score that is far from 0 in either direction (± 2 standard deviations) may represent a growth problem.

Weight, Height and BMI

CML-CP pooled population

In the naive group, at >2 years to ≤3 years, mean changes in height, weight, and BMI Z-scores were -0.57, -0.02, and 0.54 (Appendices 26, 27, and 28, respectively).

In the imatinib resistant/intolerant group, at 2 years to ≤3 years, mean changes in height, weight, and BMI Z-scores were -0.23, 0.60, and 0.07.

Advanced CML, Ph+ ALL and AML pooled population

At 2 years to ≤3 years, mean changes in height, weight, and BMI Z-scores were -0.51, 0.07, and 0.14, respectively.

Bone Growth and Development-Related AEs

In the **CML-CP pooled population**, bone growth and development AEs (any grade) were reported in 7 (8.3%) and grade 3-4 were reported in 2 (2.4%) of the naive subjects. Drug-related AEs were reported in 2 (2.4%) of subjects. The AEs reported were gynecomastia (1 subject) and growth retardation (1 subject).

In the imatinib resistant/intolerant group, bone growth and development AEs (any grade) were reported in 6 (13.0%) and grade 3-4 were reported in 1 (2.2%). Drug-related AEs were reported in 4 (8.7%) subjects. The AEs reported were epiphyses delayed fusion (1 subject), osteopenia (1 subject), gynecomastia (1 subject), growth retardation, epiphyses delayed fusion, osteoporosis (3 events in 1 subject).

In the **advanced CML, Ph+ ALL and AML pooled population**, 1 (1.7%) subject had growth retardation and foot fracture AEs which were not drug-related AEs.

Intrinsic and Extrinsic Factors

The frequencies of all-causality and drug-related AEs in the pooled CML and the advanced CML, Ph+ ALL and AML populations for subgroups of age, gender, race, region, and Karnofsky/Lansky performance status were similar to the AE frequencies in the overall pooled CML and advanced CML, Ph+ ALL and AML populations. Numerical differences in frequencies of all-causality AEs of any grade in dasatinib-treated subjects were observed in some subgroups. These differences are of limited interpretability due to low sample sizes and event rates, and do not alter the overall safety profile of dasatinib in these subgroups

Safety of Dasatinib Powder for Oral Suspension

In study CA180226, 33 paediatric (0 to 18 years of age) treatment naive CML-CP subjects were enrolled in an expanded cohort to receive dasatinib PFOS, as an age-appropriate formulation. The dose of dasatinib administered in PFOS formulation was 72 mg/m2 and subjects in this cohort were required to take dasatinib PFOS formulation for a minimum of 12 months. After 12 months, those subjects who remained on study were allowed to switch to take dasatinib tablet formulation if they chose.

The median duration of dasatinib PFOS therapy in CA180226 was 12 months and the median daily dose was 71.26 mg/m2/day. Twenty-two subjects (66.7%) had PFOS to tablet change, while 6 subjects continue to receive PFOS.

No clinically relevant safety concerns were noted in treatment-naive paediatric subjects treated with tablets or with PFOS during the first year of treatment. No differences in the safety profile were noted between tablets and PFOS.

- No deaths or drug-related SAEs were reported in naive CML-CP subjects treated with PFOS.
- AEs leading to treatment discontinuation were reported in 3 (3.6%) subjects. All of these AEs (drug hypersensitivity, leukemia, and leukemia recurrent) were Grade 3-4 and subjects discontinued due to AEs during the first year of treatment. Only 1 subject discontinued treatment due to a drug-related AE (Grade 3 drug hypersensitivity). The subject's hypersensitivity reaction was treated and resolved thereafter.
- For those subjects who switched dasatinib dosing from PFOS to tablet, rates and severities before and after the switch were decreasing as expected over the course of the treatment for all AEs and SAEs and study drug-related AEs and SAEs.
- Bone growth and development AEs related to study drug were reported in 2 (2.4%) subjects naive CML-CP subjects (1 subject each receiving PFOS and tablet); neither of these AEs was severe in intensity.

Laboratory findings

Functionally, the haematological AEs may represent rapidly progressive serious situations (also) in children, but in CML-CP the summary of On Treatment Grade 3 or 4 Laboratory Abnormalities (Table 3.1-1 and 3.2.3-1) illustrate neutropenia as the most frequent – and well-known and manageable situation at specialized departments where these patient are followed. The risk of grade 4 thrombopenia in a child pose probably in most instances a less risk than in an adult, and in particular elderly patient due to less risk of a vascular component for bleeding. The fact that all patients in CP are alive is an indirect parameter to support the point of view of manageable handling of – also laboratory - grade 3-4 AEs in children on dasatinib treatment. Treatment with dasatinib in paediatric CML-CP is associated with very limited renal, hepatic or electrolyte impact. The summary of On-Treatment grade 4 abnormalities indicate a trend to more affected patients in the imatinib treated group, but minor differences and most less than 5%, except neutropenia. The results add value to the safety of dasatinib treatment, at the recommended dosage, for the applied indication.

Safety in special populations

The clinical studies in paediatric Ph+ positive leukaemias, and most relevantly assessed in chronic phase chronic myeloid leukaemia do not indicate any association to efficacy or safety and intrinsic or extrinsic factors. The interpretation is restricted by some precaution due to the limited patient population. In particular the very young patients, the number of Black / African descendants are very

few. Still, no data indicate a relation of extrinsic factors in adults, and the age distribution must accommodate to the rarity of patients and meaningful reason to suppose an impact pathophysiological of young age, provided the same dosing effect.

Amongst PFOS treated children, two patients discontinued due to leukaemia/leukaemia relapse (CML) during treatment, within the first year. The disease progression rate on dasatinib / imatinib in the DASISION study (258 patients, each arm) were at two years: 5/7%, and the treatment failure (no remission) rate 3/4%. Progression or treatment failure (combined) at five years in the DASISION study was reported to be 11/14% for dasatinib / imatinib treatment, respectively. The observed "leukaemia risk" in PFOS at one year may be interpreted as 2/33 subjects or 6% at one year, which may be comparable to TKI effects observed in the DASISION study in adults. At one year is before the patients could switch to tablets and may be associated with the relatively reduced efficacy in clonal control of CML addressed previously. Responses to dasatinib PFOS observed in Study CA180226 by hematologic, cytogenetic and molecular responses support the comparability of dasatinib PFOS treatment of pediatric treatment-naive Ph+ CML-CP to tablet treatment of adult treatment-naive Ph+ CML-CP

Immunological events

Dasatinib has not been reported to cause an antibody production in treated patients. The medication may however cause immunomodulatory effects, which also may be important for the effect. Lymphocytosis after treatment with dasatinib in chronic myeloid leukaemia is prognostic for the effects on response and toxicity in adult CML patients. Patients under 12 years old do not generally have the consistent consecutive lymphocyte levels required to meet the definition of lymphocytosis, and thus, were not included in the analysis presented here. No definitive conclusion can be drawn from 2 subjects > 12 year pertaining the impact of lymphocytosis.

Safety related to drug-drug interactions and other interactions

Specific drug interaction studies have only been conducted in adults. No new information in paediatric subjects is available. The interaction with grape-fruit or juice is well known to increase the exposure to dasatinib by an inhibition of CYP3A4. The same must be an interaction in children, and some more emphasis is suggested in the PI, than already stated.

Discontinuation due to AES

Discontinuations due to AEs in paediatric Ph+ leukaemia occur with an acceptable incidence depending on diagnostic population. In particular in the chronic phase of disease, discontinuation regardless of causality and not by any particular cause occurred in less than 5%. In both the naive and imatinib resistant/intolerant groups no more than 1 subject reported an AE leading to discontinuation for any particular preferred term. The result is based on an acceptable number of patients to support the indication.

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

Clinical safety in adult CML patients involve aspects like cardiac effects, effusions, infections and bone marrow insufficiency, among many others, although manageable. The results on clinical safety in children aged 1-18 years-old, exposed in the majority to the medication in more than two years, with CML-CP for the assessment of dasatinib in 84 newly diagnosed and in 46 imatinib treated have not identified novel issues, and the most frequent AE are dispersed over different manifestations like headache, nausea, stomach and intestinal discomfort, physical disability, skin inconveniences and in particular leuko-neutropenia, thrombocytopenia and anaemia, and a risk of infections – all of which affect quality of life in young patients.

The overall safety profile of SPRYCEL in the paediatric population was similar to that of the adult population, regardless of formulation, with the exception of no reported pericardial effusion, pleural effusion, pulmonary oedema, or pulmonary hypertension in the paediatric population. Of the 130 SPRYCEL-treated paediatric subjects with CML-CP, 2 (1.5%) experienced adverse reactions leading to treatment discontinuation (see SmPC section 4.8.)

Dasatinib has a myelosuppressive effect. The difference compared to adult patients is that the AEs may more rapidly progress from a mild to a severe clinical situation – infections, diarrhoea possibly most important. Unexpectedly, no pleural (or other effusions) were observed in newly diagnosed patients, despite an exposure in most patients of more than two years. The pattern of AEs were not significantly different in previously imatinib treated patients.

Even though merely all patients experience some AE, the minor part are severe, and in CML-CP leads to treatment discontinuation in less than 5%. Severe and fatal AEs were reported more frequently in advanced phase CML and Ph+ ALL than chronic phase CML as would be expected based on the underlying disease. In the CML-CP pooled population, the incidence of Drug-related Serious Adverse Events can be considered low and most events concern haematological toxicity or fever/infection. In this population, 4 (8.7%) deaths may appear significant but it is noted that all the cases were reported in the imatinib resistant/intolerant group. All subjects had progressed and deaths occurred after 30 days from last dose.

In paediatric trials of SPRYCEL in imatinib-resistant/intolerant paediatric patients and treatment-naive paediatric patients after at least 2 years of treatment, treatment-related adverse events associated with bone growth and development were reported in 6 (4.6%) patients, one of which was severe in intensity (Growth Retardation Grade 3). These 6 cases included cases of epiphyses delayed fusion, osteopaenia, growth retardation, and gynecomastia (see SmPC section 4.4. and 5.1). These results are difficult to interpret in the context of chronic diseases such as CML, and require long-term follow-up (see RMP).

Attention should be paid to hormonal effects or cardiac toxicity during long-term treatment, and any impact is expected to be captured by PSUR. (Thyroid-) Hormonal adverse events are mentioned in the PI as a potential rare event. Aspects on male fertility, in an individual assessment and involving parents, as well as the adolescent subject for semen deposition before treatment is addressed in the SmPC (section 4.6). The point of view on childhood CML as a separate disease (in a major part) of children compared to adults, and the attitude towards a more aggressive treatment strategy from diagnosis has not been supported by the results obtained on safety in the studies presented.

Results on safety of the oral suspension, PFOS in CML-CP were pooled with tablet treated patients.

In the paediatric CML studies, the rate of laboratory anomalies was consistent with the known profile for laboratory parameters in adults.

Cardiac effects and other side effects of dasatinib therapy in patients less than 18 years of age will continue to be followed by means of routine pharmacovigilance.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile in paediatric patients was comparable to the safety profile in adults. Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Myelosuppression
	Fluid Retention
	Bleeding Related Events
	QT Prolongation
	Pregnancy Related Malformative or Foeto/ Neonatal Toxicity
	PAH
Important potential risks	Severe Hepatotoxicities
	Direct Cardiotoxic Effects (eg, Cardiomyopathy)
	Growth and developmental disorders and disorders of bone mineral metabolism
	Toxic Skin reactions
	CYP3A4 Drug Interactions
	Reactivation of HBV infection
	Nephrotic Syndrome
Missing information	Carcinogenicity
	Pediatric data:
	- for patients < 1 yr
	- for Ph+ ALL patients <18 yr
	Reproductive and lactation data
	Data in ethnic groups

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks: Myelosuppression	SmPC Section 4.2 Recommended starting dosage distinct for CP CML, and AP and BP CML and for Ph+ ALL. Dose adjustment guidelines for myelosuppression. SmPC Section 4.2 Dose Adjustment For Adverse Reactions with specific risk information and interventions or management. SmPC Section 4.4 Special Warnings and Precautions with special risk information SmPC Section 4.8 Undesirable Effects with specific information on related AEs, monitoring, management and/or reversibility based on clinical trial and post-marketing experience.	NA
Fluid Retention	SmPC Section 4.2 Recommended starting dosage distinct for CP CML, and AP and BP CML and for Ph+ ALL. Dose adjustment guidelines for non-haematologic AEs in general and pleural effusion in particular. SmPC Section 4.2 Dose Adjustment For Adverse Reactions with specific risk information and interventions or management. SmPC Section 4.4 Special Warnings and Precautions with special risk information SmPC Section 4.8 Undesirable Effects with specific information on related AEs, monitoring, management and/or reversibility based on clinical trial and post-marketing experience.	NA
Bleeding Related Events	SmPC Section 4.2 Recommended starting dosage distinct for CP CML, and AP and BP CML and for Ph+ ALL. SmPC Section 4.2 Dose Adjustment For Adverse Reactions with specific risk information and interventions	NA

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	or management	
	SmPC Section 4.4 Special Warnings and Precautions with special risk information	
	SmPC Section 4.8 Undesirable Effects with specific information on related AEs, monitoring, management and/or reversibility based on clinical trial and post-marketing experience.	
QT Prolongation	SmPC Section 4.2 Recommended starting dosage distinct for CP CML, and AP and BP CML and for Ph+ ALL. Dose adjustment guidelines for non-haematologic AEs in general	NA
	SmPC Section 4.2 Dose Adjustment For Adverse Reactions with specific risk information and interventions or management	
	SmPC Section 4.4 Special Warnings and Precautions with special risk information	
	SmPC Section 4.8 Undesirable Effects with specific information on related AEs, monitoring, management and/or reversibility based on clinical trial and post-marketing experience.	
Pregnancy Related Malformative or Foeto/ Neonatal Toxicity	SmPC Sections 4.6 Fertility, Pregnancy and Lactation with specific risk information and interventions or management	NA
	SmPC Section 5.3 Preclinical Safety Data	
Pulmonary Arterial Hypertension	SmPC Section 4.2 Dose Adjustment For Adverse Reactions with specific risk information and interventions or management.	NA
	SmPC Section 4.4 Special Warnings and Precautions with special risk information	
	SmPC Section 4.8 Undesirable Effects with specific information on related AEs, monitoring, management and/or reversibility based on clinical trial and post-marketing experience.	

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Potential Risks: Severe Hepatotoxicities	SmPC Section 4.2 Recommended distinct starting dosages by indication. Guidelines for dose withholding or termination with non-haematologic severe AEs. SmPC Section 4.4 Special Warnings and Precautions with special risk information SmPC Section 4.8 Undesirable Effects with specific information on related AEs, monitoring, management, interventions and/or reversibility based on clinical trial and post-marketing experience. SmPC section 5.3 pre-clinical safety data	NA
Direct Cardiotoxic effects (eg, cardiomyopathy)	SmPC Section 4.2 Recommended distinct starting dosages by indication. Guidelines for dose withholding or termination with non-haematologic severe AEs. SmPC Section 4.4 Special Warnings and Precautions with special risk information SmPC Section 4.8 Undesirable Effects with specific information on related AEs, monitoring, management, interventions and/or reversibility based on clinical trial and post-marketing experience. SmPC section 5.3 Pre-clinical safety data	NA
Growth and Development Disorders and Bone Mineral Metabolism Disorders	SmPC Section 4.8 Undesirable Effects with specific information on related AEs, monitoring, management, interventions and/or reversibility based on clinical trial and post-marketing experience.	NA
Toxic skin reactions	SmPC Section 4.8 Undesirable Effects with specific information on related AEs, monitoring, management, interventions and/or reversibility based on clinical trial and post-marketing experience.	NA
CYP3A4 Drug interactions	SmPC Section 4.4 Special Warnings and Precautions with special risk information	NA

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction	
	SmPC Section 4.8 Undesirable Effects with specific information on related AEs, monitoring, management, interventions and/or reversibility based on clinical trial and post-marketing experience.	
HBV Reactivation	SmPC Section 4.4 Special Warnings and Precautions with special risk information	DHPC issued in EU by 11 April 2016.
	SmPC Section 4.8 Undesirable Effects with specific information on incidence and outcomes	
	Patient Leaflet with specific patient information to reflect Sections 4.4 and 4.8 above.	
Nephrotic Syndrome	SmPC Section 4.8 Undesirable Effects	NA
Missing Information		
Carcinogenicity,	SmPC Section 5.3 Preclinical safety data	NA
Paediatric data	SmPC Section 4.2 Posology and Method of administration (Safety and efficacy of dasatinib in paediatric population) The safety and efficacy of SPRYCEL in children below 1 year of age not yet been established. The safety and efficacy of SPRYCEL in children and adolescents below 18 years of age with Ph+ ALL have not yet been established.	NA
Reproductive and lactation data	SmPC Sections 4.6 Fertility, Pregnancy and Lactation with specific risk information and interventions or management	NA
	SmPC Section 5.3 Preclinical safety data	
Data in ethnic group	Currently risk minimization measures for missing information on ethnic groups and dasatinib use are not addressed in the SmPC.	NA

Conclusion

The CHMP and PRAC considered that version 15.3 of the risk management plan is acceptable.

The applicant is reminded that information of potential for off-label use of the PFOS to the adult population for which this indication is not accepted should be considered during the procedure II/59. The applicant is further reminded that the PFOS formulation and tablets are not bioequivalent and dosing in milligrams for the two Sprycel formulations will be different for the children of the same weight. Thus, there might be a potential for medication errors. The applicant should consider whether the safety specification should be amended to include the risk of medication errors, and propose risk minimisation measures as necessary.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Significance of paediatric studies

The CHMP is of the opinion that CA180038 and CA180018, which are contained in the agreed Paediatric Investigation Plan, P/0118/2013 have been completed after 26 January 2007, are considered as significant.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH is seeking to add a paediatric indication to the Ph+ chronic phase CML in the indication.

3.1.2. Available therapies and unmet medical need

In paediatric patients, imatinib is the drug of choice and continued until lack of response or intolerable side effects. The opportunity to pause TKI in case of many years in deep MR, reflecting a functional cure, as in adults has not been proven in children. HSCT is considered in case of disease progression, provided a suitable sibling or unrelated donor, but associated with a risk of mortality and chronic morbidity, justified by the cure rate of 70-80%. Alternative monotherapy like interferon-alfa is rarely used in CML anymore, due to less efficacy and more safety issues than TKI, although without long term side-effects. Introduction of 2nd generation TKI like dasatinib may overcome imatinib resistance, relapse and intolerance and thereby postpone or eliminate the need for HSCT, with favourable prognosis (in adults).

It is therefore an unmet need to have a second line treatment or an alternative first line treatment in CML-CP with a disease-specific TKI. An improved OS has not been demonstrated in adults comparing imatinib and dasatinib, but dasatinib do generally induce more rapid CyR and MR than imatinib in TKI naïve patients. The administration of tablets to small children is a well-known obstacle, which may improve by introduction of a powder for oral suspension (PFOS) of dasatinib. Results are presented as well by PFOS treatment in newly diagnosed, paediatric patients.

3.1.3. Main clinical studies

Study CA180226 is considered the pivotal trial. It is an open label, Phase 2 worldwide, multi-centre trial evaluating the efficacy and safety in three cohorts below age 18years: 1: imatinib resistant or intolerant CML-CP (n=29), 2: AP, BC or Ph+ acute leukaemia, who are resistant / intolerant to or relapsed after imatinib treatment (n = 58) and 3: newly-diagnosed CML-CP (TKI-naive), divided in patients for tablet treatment (3a, n=51) or PFOS (3b, n=33). After one year treatment, patients in group 3b may use tablets instead of PFOS. The dosage in CML-CP (cohort 1 and 3a) was 60 mg dasatinib/m2 as tablet (which may be dispersed), or in cohort 3b PFOS 72 mg/m2 once daily. Dosing was 80 mg/m2 QD in cohort 2, reasoned by the much more aggressive disease biology. Study start was 20-03 2009, data-base lock 04-11 2016 in cohort 1, cohort 2 was terminated by MDC due to lack of efficacy, and cohort 3 is ongoing. By the time of database closure, in Cohort 3A (tablet dosing), 37 subjects (72.5%) remained on treatment, and 14 subjects (27.5%) withdrew from treatment and were in follow-up. In Cohort 3b (PFOS dosing), 24 subjects (72.7%) remained on treatment, and 9 subjects (27.3%) were in follow-up.

Study CA180018 is an open label, phase 1, dose-escalation study, which included imatinib resistant/intolerant patients (n=17). Some integrated efficacy data from Studies CA180018 and CA180226 are presented in the application on subjects with imatinib-resistant, imatinib-intolerant (n=46 in total), and imatinib-resistant/intolerant CML-CP and on subjects with advanced CML. Efficacy results for newly diagnosed subjects with treatment-naive CML-CP are from Study CA180226.

3.2. Favourable effects

Newly diagnosed CML-CP patients:

Results are presented separately for cohort 3a (tablet, n=51) and 3b (PFOS, n=33) and given in classic efficacy terms in CML treatment, by criteria adopted from treatment in adult CML. For MCyR by 6 months: 90/91%, at 12 months: 98/94%. CCyR by 6 months 67/70%, at 12 months 96/88%, by 24 months: 96/91% and at any time: 96/91%. MMR by 6 months: 31/18%, at 12 months: 57/46%, by 24 months: 75/64% and at any time until data base lock: 88/67%. The deep MR (MR4) was achieved by 6 months in 3.9/3.0%, at 12 months 21.6/9.1%, by 24 months 45/30% and at any time 53/36%. The complete MR was obtained at any time in 43/9%. Accordingly, a hematologic complete response was confirmed in 100/91%, unconfirmed achieved in 100/94%. Five children (9.8%) had progressive disease by tablet treatment, one patient (3%) by PFOS treatment. A total of 14 patients (27.5%) and 9 patients (27.3%) were off-treatment in cohort 3a and 3b, respectively.

Imatinib resistant/intolerant CML-CP patients:

Results are presented separately for imatinib resistant and imatinib intolerant patients (n=46), for the same parameters of efficacy. For MCyr by 3 months: 56/80%, by 6 months: 79/90%, at 12 months: 85/100% and by 24 months of treated patients: 85/100%. The CCyR by 3 months were 44/60%, by 6 months 74/80%, at 12 months 77/80% and by 24 months 79/90%. The MMR rate by 3 months 15/20%, by 6 months 27/30%, at 12 months 41/40%, by 24 months 53/60%. CHR was confirmed at any time in 93% and unconfirmed in 100% in cohort 1 in study CA180226 (n=29). A total of 7 patients (15%) had progressive, refractory or resistant disease, and 31 patients (67%) were off treatment at data base closure in November 2016.

3.3. Uncertainties and limitations about favourable effects

Uncertainty regarding the switch from dasatinib tablets (60 mg/m^2) to PFOS 90 mg/m^2 treatment is addressed in the PI and will be investigated in a PK "window study" in which eligible subjects already on dasatinib tablets (60mg/m^2) would switch to PFOS (90 mg/m^2) during which time the necessary PK samples would be collected. The Applicant has performed an additional detailed feasibility assessment, and it is expected that the CSR for this study could be available in 1Q 2020.

The PFOS formulation and tablets are not bioequivalent and dosing in milligrams for the two Sprycel formulations will be different for the children of the same weight which is a concern for potential medication errors. Appropriate dosing instructions on switching are included in the PI. The MAH will take appropriate measures to minimise the risk of medication errors including a further revision of the packaging to include a warning about the non-bioquivalence between formulations.

3.4. Unfavourable effects

Almost all experienced AEs among newly diagnosed patients (99%), in 66% they were severe. Likewise in previously treated patients 96% had an AE of any grade, in 63% the AE was grade 3-4. The pattern of AEs in newly diagnosed was very similar to treatment by dasatinib in adults, dominated by (all grade / grade 3-4 in %) myelosuppression (54/36%), infections (79/16%), gastrointestinal (76/10%), skin (60/4%), general disorders (62/6%) and headache appearing all grades in 46%, severe in 1.2%. Musculoskeletal, respiratory AEs were frequent but seldom severe. In previously TKI-treated patients registration of severe AE were more frequent in musculoskeletal (8.7%), nervous system disorders (headache 8.7%), but less severe in myelosuppression (20%). Infections, gastrointestinal and other AEs were similar appearing as in newly diagnosed patients. Cardiac

dysfunction and disorders were registered in less than 3% in both groups, less than grade 3. In both patient populations laboratory findings reflected the cytopenias induced by TKI.

3.5. Uncertainties and limitations about unfavourable effects

There is limited data on long-term exposure. It is noted that in the CML-CP pooled population 76 subjects (58.5%) remained on treatment at the data lock date. Information on long term exposure will be collected through PSURs.

3.6. Effects Table

Table 30: Effects Table for dasatinib in the paediatric population

Effect	Short Description	Unit	Newly diagnosed CP-CML n=51	Newly diagnosed CP-CML n=33	Imatinib resistant or intolerant CP-CML n=46
Favourable Effects			dasatinib tablets	dasatinib suspension PFOS	dasatinib tablets
Complete CyR at one year		%	96	88	76
Major MR at one year		%	57	46	41
Complete MR at any time		%	43	9	24
Unfavourable Effects			Newly diagnosed (pooled) n=84 All / grade 3-4		Prior imatinib treatment n=46 All / grade 3-4
Neutropenia		%	30 / 25		15 / 15
Thrombopenia		%	24 / 13		13 / 4
Diarrhoea		%	49 / 1		61 / 4
Nausea		%	36 / 0		39 / 0
Pain extremity		%	30 / 0		52 / 2
Headache		%	46 / 1		61 / 9
Upper respirat.tract infection		%	32 / 1		26 / 0
Pyrexia		%	42 / 5		41 / 0
Rash		%	30 / 0		33 / 0
Hypokalaemia		%	3.6 / 3.6		0 / 0

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Since the efficacy of dasatinib in terms of haematological responses is in line with the known efficacy of the product; the lack of bioequivalence of the PFOS and dispersed tablets with the reference tablets

has been addressed with a PFOS dose increase to 90 mg/m^2. The dosage of 90 mg/m^2 PFOS is now satisfactorily justified for children < 45 kg from 1 year of age and day 1 in treatment with dasatinib.

Paediatric and adults patients > 45 kg are likely to have similar physiology and for patients > 45 kg PFOS dose of 120 mg is proposed in line with the findings in the adult BE study. This is reflected in the SmPC.

The safety profile in paediatric patients was comparable to the safety profile in adults. Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

3.7.2. Balance of benefits and risks

The administration of tablets to small children is a well-known problem, which is addressed by the introduction of a powder for oral suspension (PFOS) of dasatinib.

The efficacy and safety of dasatinib PFOS is demonstrated and an appropriate dose is determined.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Sprycel 10 mg/mL powder for oral suspension for the treatment of paediatric patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP), or with Ph+ CML-CP resistant or intolerant to prior therapy including imatinib, is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Sprycel is not similar to Tasigna (nilotinib) and Iclusig (ponatinib) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of, Sprycel 10 mg/mL powder for oral suspension is favourable in the following indication:

Sprycel is indicated for the treatment of paediatric patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML CP), or with Ph+ CML CP resistant or intolerant to prior therapy including imatinib.

The CHMP therefore recommends the extension of the marketing authorisation for Sprycel subject to

the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0118/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In accordance with Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed paediatric investigation plan P/0118/2013 have been completed after the entry into force of that Regulation.

In addition, CHMP recommends the variation to the terms of the marketing authorisation concerning the following changes:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

To include the treatment of paediatric patients with newly diagnosed Ph+ CML in chronic phase

(Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib for Sprycel film-coated tablets. Sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the new indication and its relevant posology, to add a warning on effects on growth and development in the paediatric population and to update the safety information.

The Annex A, Annex II, Labelling, Package Leaflet and RMP (version 15.3) are updated in accordance.

Appendix

1. CHMP AR on similarity dated 26 April 2017.